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British Heart Journal

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British Cardiac Society

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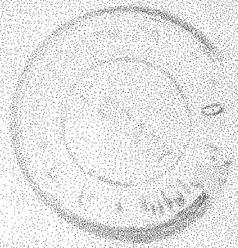

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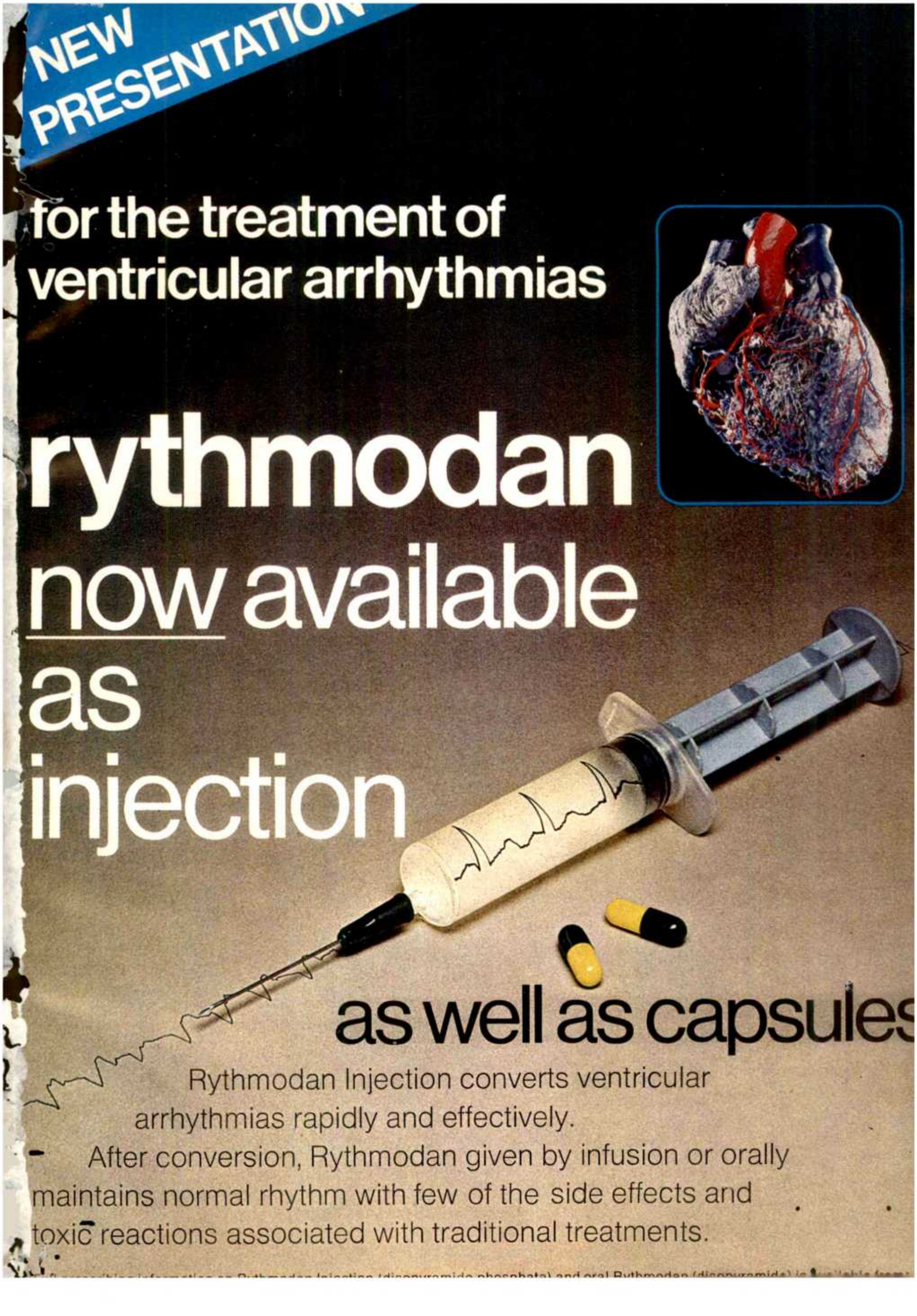

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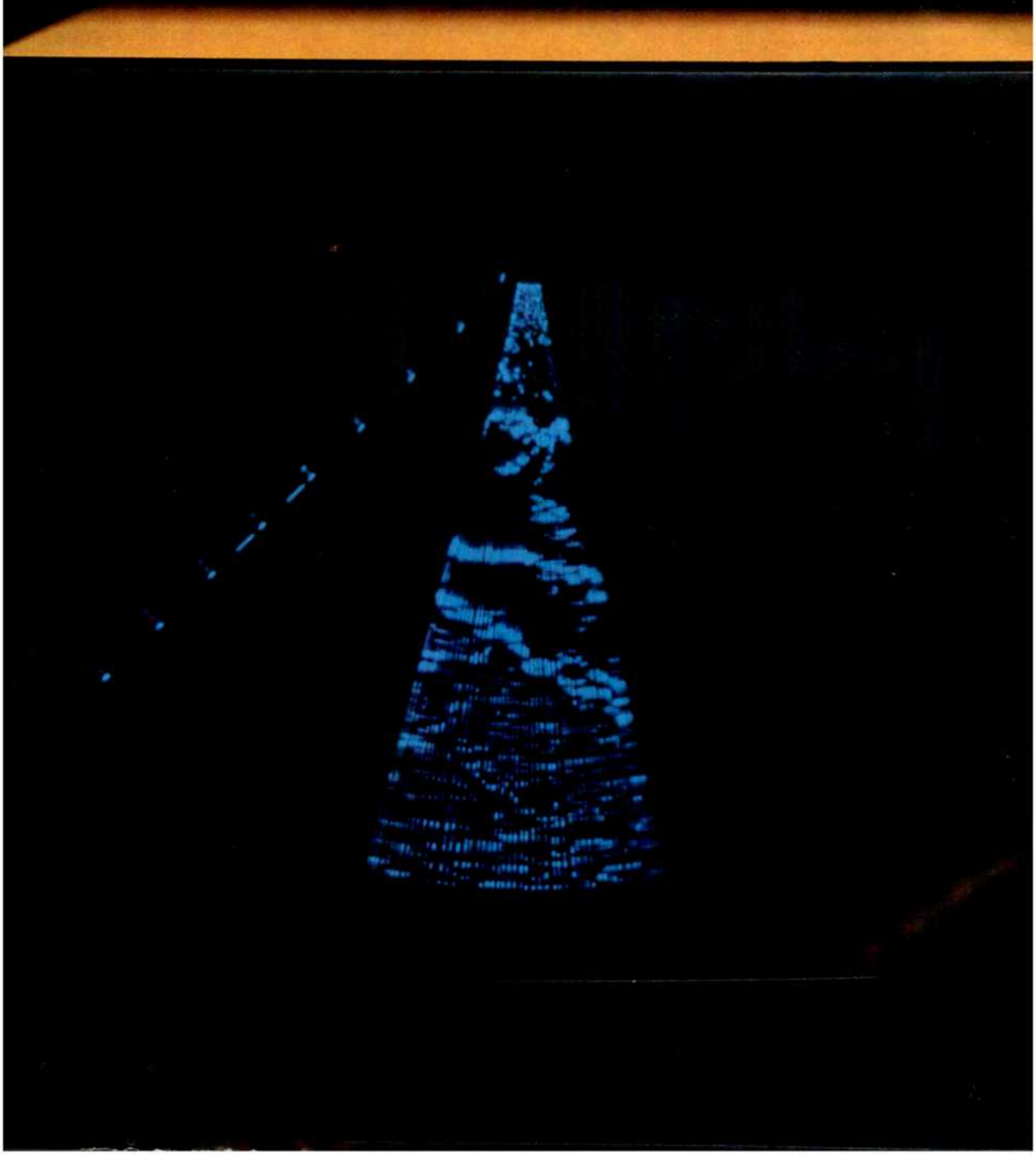

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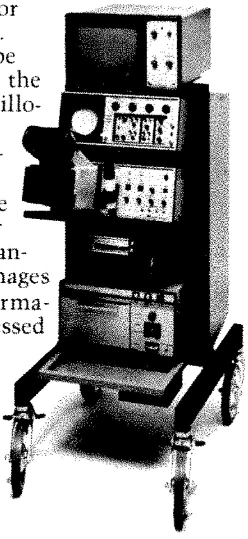

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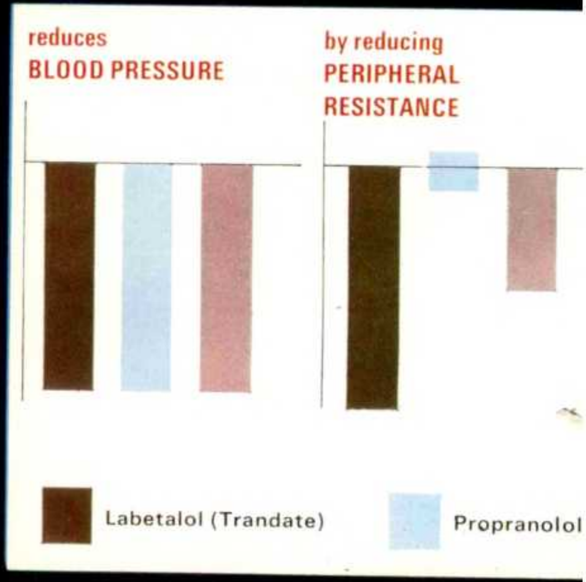

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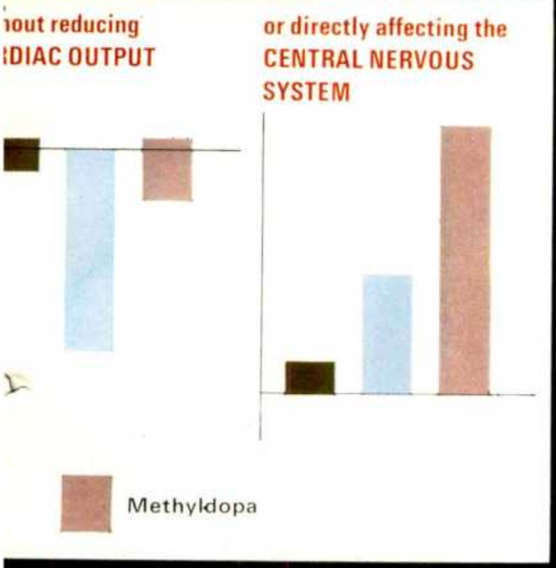

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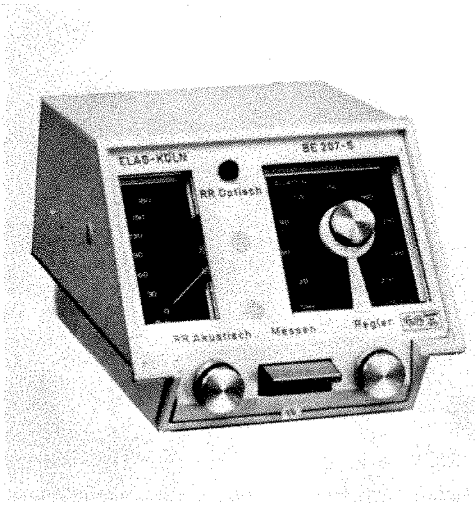

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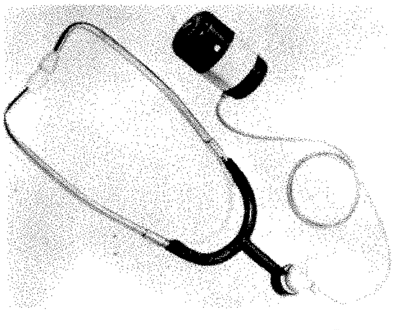

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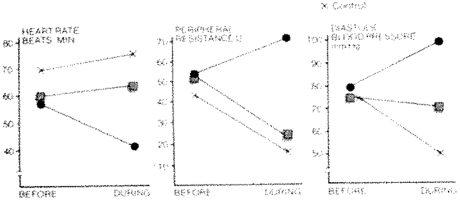

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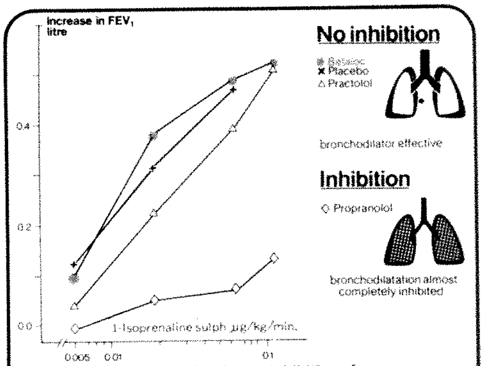

Asthmatic patients: showing no inhibition of isoprenaline effect by Betaloc, compared with almost complete inhibition by non-selective propranolol.

[1] (1975) *Acta pharmacol et toxi* Suppl. V, 39-68 University of Gothenburg, Sweden.

[2] Clinical Report (1975), University of Gothenburg, Sweden.

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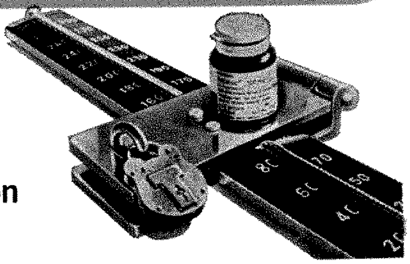

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1. Lancet, 1973, ii, 399 2. Lancet, 1973, ii, 404 3. Amer. Heart J., 1976, *91*, 58
4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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British Heart Journal, 1977, **39**, 701–705

Mid ventricular obstruction in hypertrophic obstructive cardiomyopathy
New diagnostic and therapeutic challenge

RAUL E. FALICOV AND LEON RESNEKOV

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A recent editorial by Shah (1975) outlined the eventful and controversy-filled saga of hypertrophic obstructive cardiomyopathy (HOCM) (idiopathic hypertrophic subaortic stenosis, muscular subaortic stenosis, obstructive asymmetric septal hypertrophy). Concepts of the anatomical and pathophysiological mechanism(s) of left ventricular outflow obstruction present in this disease have evolved slowly over the years. At first, obstruction was attributed to a circular muscle band in the left ventricular outflow tract (Brachfeld and Gorlin, 1959; Brock, 1959; Cohen *et al.*, 1964) but later this view was felt to be too simple, overlooking the fact that the left ventricle unlike the right does not have a true muscular outflow tract (Shah, 1975). Whether a true intraventricular pressure gradient was actually even present in hypertrophic cardiomyopathy was subsequently questioned by Criley *et al.* (1965). They explained recorded subaortic pressure gradients as being caused by entrapment of the catheter, based on the demonstration that high subendocardial pressures transmitted to a catheter embedded in the trabeculated left ventricular apex result in artefactual gradients (Morrow *et al.*, 1965; Dieudonné, 1966). Further consideration of the problem indicated that systolic outflow obstruction does occur in hypertrophic cardiomyopathy, coexisting in some instances with artefactual gradients caused by catheter entrapment (Adelman and Wigle, 1968). The criteria for discrimination between true and artefactual intraventricular gradients were described by Ross *et al.* (1966) and by Wigle *et al.* (1967) and were based mainly on recording a high left ventricular inflow systolic pressure (obtained by withdrawal of a transseptal catheter from the left ventricle to the left atrium) as the primary evidence for true obstruction. Angiographic observations had already suggested that the anterior leaflet of the mitral valve could be an important cause of ventricular obstruction by its abnormal apposition to the septum during systole. Outflow obstruction in hypertrophic cardiomyopathy was, therefore, defined by recording a systolic pressure gradient between the inflow and outflow portions of the left ventricle; the finding of high apical pressures in the presence of low left ventricular inflow pressures was then to be interpreted as catheter entrapment artefact resulting from the vigorous ventricular emptying during systole.

More recently, echocardiographic observations have provided additional information regarding the possible causes of systolic outflow obstruction in hypertrophic obstructive cardiomyopathy. The septum is disproportionately thicker than the posterior wall by a ratio of 1·3 or more (Henry *et al.*, 1973a) and the anterior mitral leaflet moves in systole toward the septum (Shah *et al.*, 1969). The length and degree of the systolic apposition of the mitral leaflet against the septum have correlated well with outflow gradients found at catheterisation (Henry *et al.*, 1973b), though lack of correlation has been noted by other authors (Rossen *et al.*, 1974). The precise mechanisms for the systolic apposition of the anterior mitral leaflet against the septum are not clearly understood, being attributed to malalignment of the anterior papillary muscle (Reis *et al.*, 1974) or to a Venturi effect on the left ventricular outflow tract (Wigle *et al.*, 1971) produced by the abnormal anatomy and contraction patterns. As further evidence of the role of the mitral valve, Cooley *et al.* (1973) showed disappearance of outflow gradients after mitral valve replacement with a low profile prosthesis in several patients. Both echocardiographic and haemodynamic observations, then, appeared closely correlated and seemed to have shown, with reasonable certainty, the precise site and structures involved in producing left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy.

Recent findings, however, suggest that the pathophysiological and anatomical alterations in hypertrophic obstructive cardiomyopathy may be wider ranging than previously thought. In a recent, comprehensive review of 40 postmortem hearts of patients who had hypertrophic obstructive cardiomyopathy, Roberts and Ferrans (1975) found that ventricular septal thickness was not greater than free wall thickness in 7 hearts (18%) negating in these the presence of asymmetric septal hypertrophy in the anatomical sense. Septal thickness was also greatest in all of their cases midway between the aortic valve cusps and the left ventricular apex, rather than in the outflow tract itself. In 11 hearts (28%) there was no thickening of the mural endocardium in apposition to the anterior mitral leaflet, suggesting that systolic mitral valve apposition to the septum had not been a prominent feature during life. Thirty-three patients had had cardiac catheterisation studies, and a subaortic gradient was shown in 20, but there is no mention by the authors of the route of left ventricular catheterisation, or whether left ventricular inflow tract pressures were measured.

We have recently reported 2 patients (Falicov *et al.*, 1976) in whom left ventricular obstruction was present in the mid ventricular area, rather than at the junction of the inflow and outflow tracts. In the first patient, the diagnosis was made by postmortem examination after sudden death with unrelieved obstruction 6 months after septal myotomy-myectomy of the left ventricular outflow tract by the transaortic approach. In the second patient, a two-catheter left ventricular study (transseptal and retrograde) showed no gradient between the inflow and outflow tracts, but a high, true pressure gradient between the apex and the inflow and outflow tracts; the gradient was present at a sphincter-like severe narrowing in the mid ventricular area. In retrospect, identical angiographic features were present in the first patient. The second patient's echocardiogram showed asymmetric septal hypertrophy but no systolic anterior motion of the mitral leaflet in spite of a resting 100 mmHg intraventricular systolic gradient. We suggested that obstruction in these patients was caused by a true muscular stenosis in the mid portion of the left ventricle. Since the abnormality was in the mid portion of the ventricle and the anterior leaflet of the mitral valve was not participating in the obstruction, neither outflow septal myectomy nor mitral valve removal alone could reasonably be expected to relieve the transventricular pressure gradient. On the other hand, mid ventricular septal resection and/or papillary muscle and trabecular resection might well relieve the obstruction by removing some of the hypertrophic muscular mass in the mid ventricular zone, the cause of the obstruction.

We have more recently had the opportunity of testing this hypothesis (Falicov *et al.*, 1977) in a patient with severe mid ventricular obstruction (resting systolic gradient of 75 mmHg), shown by the two-catheter technique mentioned above, and additional mitral valve stenosis as well (mitral valve area = 1·3 cm^2), thought to be rheumatic in origin. Echocardiogram showed severe, asymmetric hypertrophy of the *posterior* wall in the mid ventricular area and no systolic anterior movement of the anterior mitral leaflet. At operation, the mitral valve was resected and replaced with a Hancock porcine heterograft valve. The papillary muscles were excised as close to their bases as possible, and several hypertrophic trabeculations were resected in the mid ventricular area from the free wall as well as the septum. At postoperative catheterisation, the mid ventricular systolic gradient was reduced to one-half of its preoperative value, and the transmitral diastolic gradient was abolished.

There is, therefore, now sufficient evidence accumulated to support the concept of a spectrum of physiopathological and anatomical disorders causing left ventricular obstruction in hypertrophic obstructive cardiomyopathy, which probably relate to the heterogeneous and disorderly hypertrophic process underlying this disease. In many cases, the abnormal systolic contraction patterns and deformed geometry of the left ventricular cavity alter the direction of papillary muscle contraction and produce haemodynamic forces which attract the anterior mitral valve leaflet against the bulging septum during systole; thus, obstruction occurs at the junction of the inflow and outflow tracts. In other instances, the hypertrophic process predominates at the mid ventricular level, and the hypertrophic papillary muscles together with abnormal free wall trabeculations abut against the septum during systole to produce true muscular stenosis; there is a high pressure apical chamber, while both inflow and outflow tracts remain free of obstruction (Fig. 1). Obstruction may even be present in varying degrees at both outflow and mid ventricular levels as reported by E. D. Wigle (1976, personal communication) and may be explained by a combination of some or all the factors already mentioned.

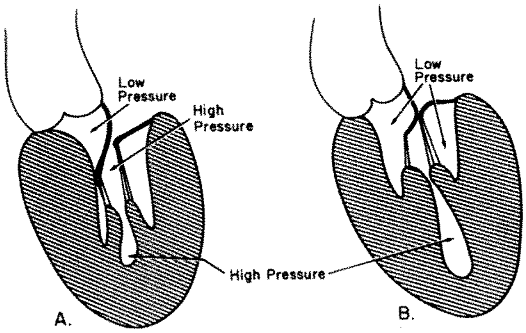

Fig. 1 *Schematic representation of the two possible sites of systolic obstruction in hypertrophic obstructive cardiomyopathy. (A) Subaortic obstruction, produced by systolic apposition of the mitral leaflet against the septum. (B) Mid ventricular obstruction, produced by muscular apposition in the mid ventricular area.*

DIAGNOSIS OF MID VENTRICULAR HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

The clinical presentation of our patients was indistinguishable from that of other patients with subaortic hypertrophic obstructive cardiomyopathy in terms of symptoms, clinical signs, and electrocardiographic features. The echocardiogram in two patients showed some suggestive features, such as the absence of true systolic anterior motion of the anterior leaflet of the mitral valve in both patients, and lack of asymmetrical septal hypertrophy in one (in fact, she had asymmetrical hypertrophy of the *posterior* wall). Thus, the presence of atypical echocardiographic features in patients with otherwise typical hypertrophic obstructive cardiomyopathy may alert the clinician to the possible presence

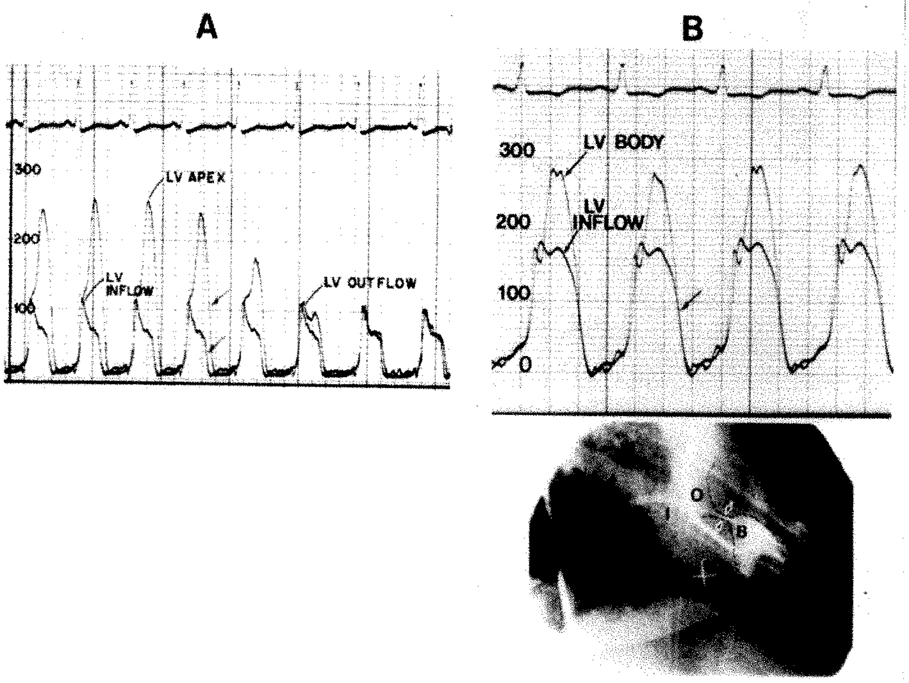

Fig. 2 *Two types of gradients in a patient with mid ventricular hypertrophic obstructive cardiomyopathy. (A) A transseptal catheter was recording left ventricular inflow tract pressures (LV inflow). A second catheter with multiple side holes had been advanced retrogradely into the left ventricular (LV) body and was pulled back into the outflow tract (LV outflow). Notice the delayed fall in LV pressure (arrows) while high pressure was being recorded, suggesting catheter entrapment. Blood could still be withdrawn from the catheter during systole, indicating that some of the side holes were free in the LV cavity, while others were trapped against the LV wall and recording subendocardial pressure. (B) In the same patient, a single, end-hold catheter was placed during a second study in the left ventricular cavity while a transseptal catheter was placed in the LV inflow tract. The fall in LV systolic pressure in both tracings occurred at the same time (arrow), blood could be withdrawn from the catheter during systole, and manual injection of contrast (bottom) outlined a blood-filled cavity surrounding the tip of the catheter, with a severe muscular narrowing immediately downstream from it (arrows). A true transventricular gradient was therefore demonstrated. I = inflow tract, O = outflow tract, B = left ventricular body.*

of mid ventricular hypertrophic obstructive cardiomyopathy.

Until more experience is accumulated, however, the mainstay for the diagnosis of mid ventricular hypertrophic obstructive cardiomyopathy rests on the typical angiographic features ('hour-glass' ventricle), together with the precise localisation of a true gradient in the mid left ventricular area. An informal survey of major cardiac catheterisation facilities in the Chicago metropolitan area, with a combined study load of over 2800 patients annually, showed that 1 per cent of patients studied over the past year had hypertrophic obstructive cardiomyopathy. Most were investigated using an aortic or brachial arterial catheter and a second catheter placed in the left ventricle by the retrograde approach; thus, no effort was made to locate the level of the gradient. We believe that in every patient studied because of suspected hypertrophic obstructive cardiomyopathy an attempt should be made to locate the site of the systolic gradient by using either the transseptal approach, in conjunction with the retrograde left ventricular approach, or the retrograde left atrial technique as proposed by Wong *et al.* (1975), with simultaneous or successive determination of left ventricular inflow, body, and outflow tract pressures. Artefactual pressure gradients are commonly encountered during catheterisation in patients with hypertrophic obstructive cardiomyopathy along with true cavity gradients; differentiation between true and false gradients is sometimes difficult, even more so now since the criterion of high versus low initial inflow pressure to distinguish between the two (Ross *et al.*, 1966; Wigle *et al.*, 1967) can no longer be considered valid. We have found several additional criteria useful in differentiating catheter entrapment from true gradients (Wigle *et al.*, 1967) and they are listed in the Table. The simultaneous recording of two intraventricular pressures is recommended for better evaluation of the magnitude of the gradients as well as the detection of the delayed fall in the left ventricular systolic pressure characteristic of catheter entrapment artefact (Fig. 2).

Table *Recognition of catheter entrapment: catheter entrapment artefacts are common in hypertrophic obstructive cardiomyopathy and coexist with true gradients*

Use catheter with end hole, no side holes
Unusual waveform
Longer duration of systole (delayed relaxation)
Inability to aspirate blood during systole
Intramyocardial staining by hand injection of contrast during systole

(Modified from Wigle *et al.*, 1967)

It is clear that more than a casual approach is needed for the detection of mid ventricular obstructive cardiomyopathy, but we believe that an effort in this direction is definitely worth while. Besides the serious practical implications regarding the surgical approach to this disease as documented in two of our patients, the determination of the actual prevalence of mid ventricular obstructive cardiomyopathy will help stimulate further thinking about the pathophysiology, diagnosis, and management of hypertrophic obstructive cardiomyopathy, a 'disease of pitfalls and paradoxes' (Spodick, 1972).

References

Adelman, A. G., and Wigle, E. D. (1968). Two types of intraventricular pressure difference in the same patient. *Circulation*, **38,** 649–655.

Brachfeld, N., and Gorlin, R. (1959). Subaortic stenosis: a revised concept of the disease. *Medicine*, **38,** 415–433.

Brock, R. (1959). Functional obstruction of the left ventricle (acquired aortic subvalvar stenosis). *Guy's Hospital Reports*, **108,** 126–143.

Cohen, J., Effat, H., Goodwin, J. F., Oakley, C. M., and Steiner, R. E. (1964). Hypertrophic obstructive cardiomyopathy. *British Heart Journal*, **26,** 16–32.

Cooley, D. A., Leachman, R. D., and Wukasch, D. C. (1973). Diffuse muscular subaortic stenosis: surgical treatment. *American Journal of Cardiology*, **31,** 1–6.

Criley, J. M., Lewis, K. B., White, R. I., Jr., and Ross, R. S. (1965). Pressure gradients without obstruction. A new concept of 'hypertrophic subaortic stenosis'. *Circulation*, **32,** 881–887.

Dieudonné, J. M. (1966). Artificial nature and site of the systolic pressure drop during inotropic stimulation of the normal ventricle. *Canadian Journal of Physiology and Pharmacology*, **44,** 829–836.

Falicov, R. E., Karunaratne, H. B., Cahill, N, and Lamberti, J. J., Jr. (1977). Hypertrophic cardiomyopathy with mid-ventricular obstruction associated with mitral stenosis: partial relief of the obstruction by papillary muscle and trabecular resection. *Journal of Catheterization and Cardiovascular Diagnosis* (in press).

Falicov, R. E., Resnekov, L. Bharati, S., and Lev, M. (1976). Mid-ventricular obstruction: a variant of obstructive cardiomyopathy. *American Journal of Cardiology*, **37,** 432.

Henry, W. L., Clark, C. E., and Epstein, S. E. (1973a). Asymmetric septal hypertrophy (ASH): the unifying link in the IHSS disease spectrum. *Circulation*, **47,** 827–832.

Henry, W. L., Clark, C. E., Glancy, D. L., and Epstein, S. E. (1973b). Echocardiographic measurement of the left ventricular outflow gradient in idiopathic hypertrophic subaortic stenosis. *New England Journal of Medicine*, **288,** 989–993.

Morrow, A. G., Vasko, J. S., Henney, R. P., and Brawley, R. K. (1965). Can outflow obstruction be induced within the normal left ventricle? *American Journal of Cardiology*, **16,** 540–546.

Reis, R. L., Bolton, M. R., King, J. F., Pugh, D. M., Dunn, M. I., and Mason, D. T. (1974). Anterior-superior displacement of papillary muscles producing obstruction and mitral regurgitation in idiopathic hypertrophic subaortic stenosis. *Circulation*, **49-50,** Suppl. II, II-181–188.

Roberts, W. C., and Ferrans, V. J. (1975). Pathologic anatomy of the cardiomyopathies. *Human Pathology*, **6,** 287–342.

Ross, J., Jr., Braunwald, E., Gault, J. H., Mason, D. T., and Morrow, A. G. (1966) The mechanism of the intraventricular pressure gradient in idiopathic hypertrophic subaortic stenosis. *Circulation,* **34,** 558–578.

Rossen, R. M, Goodman D. J., Ingham, R. E., and Popp, R. L. (1974). Echocardiographic criteria in the diagnosis of idiopathic hypertrophic subaortic stenosis. *Circulation,* **50,** 747–751.

Shah, P. (1975). IHSS-HOCM-MSS-ASH? *Circulation,* **51,** 577–580.

Shah, P. M., Gramiak, R., and Kramer, D. H. (1969). Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. *Circulation,* **40,** 3–11.

Spodick, D. H. (1972). Hypertrophic obstructive cardiomyopathy of the left ventricle. *Cardiovascular Clinics,* **4** (1), p. 133. F. A. Davis, Philadelphia.

Wigle, E. D., Adelman, A. G., and Silver, M. D. (1971). Pathophysiological considerations in muscular subaortic stenosis. In *Hypertrophic Obstructive Cardiomyopathy,* p. 63. (Ciba Foundation Study Group No. 37.) Ed. by G. E. W. Wolstenholme and M. O'Connor Churchill, London.

Wigle, E. D., Marquis, Y., and Auger, P. (1967). Muscular subaortic stenosis. Initial left ventricular inflow tract pressure in the assessment of intraventricular pressure differences in man. *Circulation,* **35,** 1100–1117.

Wong, B., Langou, R. A., Cohen, L. S., and Wolfson (1975). Retrograde catheterization of the left atrium in idiopathic hypertrophic subaortic stenosis. *American Journal of Cardiology,* **36,** 62–66.

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Invited article

British Heart Journal, 1977, **39**, 706–720

Vasodilator treatment for acute and chronic heart failure[1]

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The current status of the use of vasodilator drugs in the treatment of acute and chronic heart failure has been reviewed. It is apparent that vasodilator treatment can be used effectively in some patients with heart failure with a beneficial haemodynamic response, and that vasodilator agents are likely to find an important place in the management of such patients. Vasodilator treatment may be associated with complications and must be used with care. Though several nonparenteral vasodilator agents have been investigated, no ideal drug is yet available for the treatment of chronic heart failure. Nevertheless, it is probable that suitable drugs will emerge and find an important place in the management of such patients.

It has been shown that vasodilator therapy can improve cardiac performance in patients with heart failure, both acute and chronic. The ability of vasodilator drugs to increase cardiac performance is not related to a direct effect on the heart, since most of these agents have been shown to have no direct positive inotropic effects on the myocardium (Chatterjee *et al.*, 1973a). The two primary effects of these agents appear to be on the post-capillary capacitance bed and on the precapillary resistance bed. Vasodilator agents increase the venous capacitance, causing an increase in the relative size of the venous blood pool, a decrease in intracardiac blood volume (preload), and a decrease in systemic and pulmonary venous pressures. The other major effect of these drugs is to decrease arteriolar resistance and thus unload the heart; this unloading of the heart seems to be the most important mechanism whereby these drugs improve cardiac performance. It has been established in the isolated heart muscle preparation that with constant initial muscle length (preload), the degree of shortening is inversely proportional to afterload (Sonnenblick, 1962). This suggests that in the intact heart reduction in the afterload would result in enhanced myocardial fibre shortening and stroke volume. In relation to isolated muscle mechanics, the term afterload has been used to refer to the additional load above the preload, against which the muscle works as it shortens. To relate this concept to the intact heart, it is strictly necessary to measure wall stress during ejection, which according to the Laplace equation depends upon intraventricular pressure, wall thickness, and ventricular size and shape. This would be particularly difficult to determine during the ejection phase because of the rapidly changing relation between all these variables. A more practical and simple method of defining the load resisting ejection in the intact heart is to consider the systolic impedance. Though a precise definition of impedance involves consideration of a series of harmonics which describe pressure and flow (Milnor, 1975), an approximation can be derived from the analysis of the instantaneous relation between pressure and flow during ejection (impedance $=P/\dot{Q}$, where P and $\dot{Q}$ are instantaneous pressure and flow, respectively). Thus, a reduction in ejection impedance can be produced by a reduction in systolic pressure and/or an increase in stroke output. It is clear that ejection impedance is closely related to peripheral vascular resistance. Thus, though the vasodilator drugs which reduce peripheral vascular resistance are often referred to as 'afterload reducing agents', it is preferable to describe their effect in terms of im-

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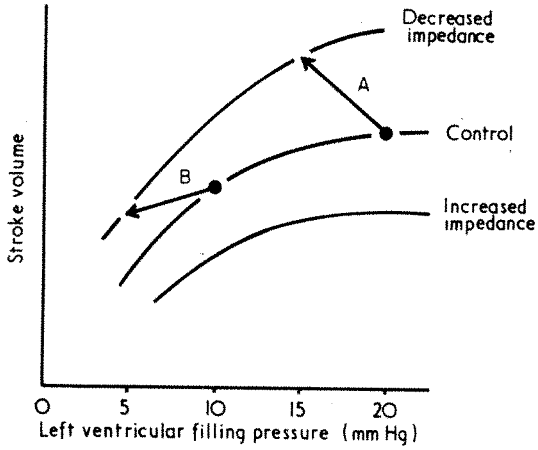

Fig. 1 *Diagrammatic illustration of the effects of changes in impedance and preload on the ventricular function curve. The control ventricular function curve shows an increase in left ventricular stroke volume with an increase in left ventricular filling pressure up to an optimal level of 15 to 20 mmHg. Vasodilator drugs, which decrease impedance, shift this curve upwards while vasopressor drugs, which increase impedance, shift the curve downwards. Line A shows a beneficial response to vasodilator therapy when the filling pressure is relatively high: the reduction in left ventricular filling pressure is accompanied by an increase in stroke volume. Line B shows a decrease in stroke volume during vasodilator therapy when initial filling pressure is low: though the reduction of impedance tends to increase stroke volume, this is offset by the further reduction in filling pressure down the ascending limb of the ventricular function curve; the net effect is a reduction in stroke volume.*

pedance reduction. Though the precise quantification of impedance is difficult, the concept is extremely valuable, and in many ways it is better to consider impedance than arterial pressure alone. For example, some patients who receive vasodilators show an increase in stroke volume and cardiac output without any change in arterial pressure. In this situation, there is an unloading of the ventricle in terms of impedance reduction, despite the lack of a fall in arterial pressure.

Although most vasodilator agents produce similar haemodynamic effects, the haemodynamic response may vary. Thus, most vasodilators have dilating effects on both the resistance and the capacitance vascular beds. However, the arteriolar resistance bed may be predominantly affected by some vasodilator drugs and the venous capacitance beds by others; other vasodilator agents possess balanced effects on these two vascular beds. The quantitative difference in the haemodynamic response to different vasodilator agents is not only related to their different pharmacological properties, but also to the types of patients being treated. Vasodilator agents may cause an increase, a decrease, or no change in left ventricular stroke volume and cardiac output, depending on the level of initial left ventricular filling pressure (Fig. 1). As a result of the curvilinear relation between left ventricular stroke volume and filling pressure, decreased aortic impedance in the patient represented by the line A is associated with an *increase* in stroke volume, despite a substantial decrease in left ventricular filling pressure. In contrast, in a patient with initially low left ventricular filling pressure (B), a further decrease in left ventricular filling pressure associated with a decrease in aortic impedance of similar magnitude may result in a *decrease* in stroke volume. Furthermore, in patients with high filling pressure, there is usually no change or a slight reduction in heart rate. In patients with a low initial filling pressure, there is often a compensatory tachycardia in an attempt to maintain cardiac output. This emphasises the importance of determining left ventricular filling pressure before vasodilator treatment is started, if the objective of treatment is to improve cardiac performance.

For the treatment of pump failure, acute or chronic, several vasodilator agents have been used with beneficial haemodynamic effects. Some of the vasodilator drugs are used intravenously, while some can be administered by other routes. In the following section, the role of vasodilator treatment in the management of pump failure, complicating acute myocardial infarction or chronic refractory heart failure, will be discussed. An attempt will be made to assess the advantages and disadvantages of the various vasodilator agents in relation to the specific objective of treatment.

Vasodilator treatment for heart failure in acute myocardial infarction

The haemodynamic effects of various vasodilator agents, including sodium nitroprusside (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973a; Chatterjee and Swan, 1973, 1974), phentolamine (Kelly *et al.*, 1973; Walinsky *et al.*, 1974; Gould *et al.*, 1974; Perret *et al.*, 1975), nitroglycerin, both intravenous and sublingual (Flaherty *et al.*, 1975; Come *et al.*, 1975; Borer *et al.*, 1975; Armstrong *et al.*, 1975a; Gold *et al.*, 1972; Williams *et al.*, 1975a), trimetaphan (Shell and Sobel, 1974), and isosorbide dinitrate (Mantle *et al.*, 1976), have been investigated in patients with acute myocardial infarction.

The haemodynamic effects of sodium nitro-

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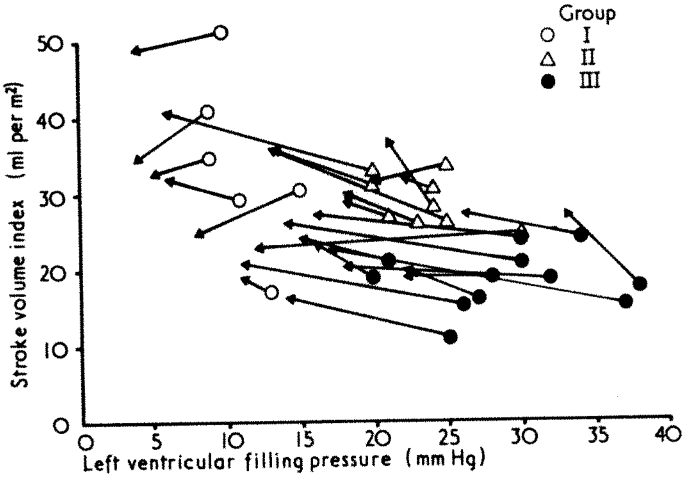

Fig. 2 *Changes in left ventricular filling pressure and stroke volume during nitroprusside infusion in a group of patients with acute myocardial infarction. Group I represents patients with an initial left ventricular filling pressure less than 15 mmHg. The patients in group II had clinically moderate left ventricular failure, with initial left ventricular filling pressure and stroke work index higher than 15 mmHg and 20 g m per m², respectively. While group III patients had severe left ventricular failure, with a left ventricular filling pressure higher than 15 mmHg and stroke work index of 20 g m per m² or less. In group II and III patients, nitroprusside infusion produced a reduction in filling pressure along with an increase in stroke volume. In group I patients with an initially low filling pressure, stroke volume usually decreased with a further reduction in filling pressure (Chatterjee and Parmley, 1976: reprinted by permission of* Progress in Cardiovascular Diseases*).*

prusside infusion in 27 patients with acute myocardial infarction are summarised in Table 1. Patients were divided into three groups on the basis of the initial left ventricular filling pressure (pulmonary artery wedge or pulmonary artery end diastolic pressure) and stroke work index. Group I included those patients with filling pressure (LVFP) less than 15 mmHg, the majority of patients being free from clinical signs and symptoms of left ventricular failure. The patients in group II had initial left ventricular filling pressures higher than 15 mmHg and a stroke work index greater than 20 g m per m² BSA; the majority of the patients in this group had frank pulmonary oedema and all had clinical and radiological evidence of left ventricular failure. Group III patients included those with LVFP greater than 15 mmHg and stroke work index of 20 g m per m² or less; all patients in this group had clinically severe left ventricular failure and frank pulmonary oedema; furthermore, the majority of patients in this group were hypotensive and several patients had clinical features of shock. The usual haemodynamic response to nitroprusside infusion in each group was a decrease in systemic and pulmonary vascular resistance, a decrease in pulmonary arterial, right atrial, and left ventricular

Table 1 *Haemodynamic effects of nitroprusside infusion in patients with acute myocardial infarction*†

No. of patients	*Group I* 6		*Group II* 9		*Group III* 12	
	C	*NP*	*C*	*NP*	*C*	*NP*
Heart rate (beats/min)	89·0 ±7·1	96·7 ±8·6	91·3 ±4·2	94·7 ±3·4	100·2 ±4·0	100·5 ±4·8
Mean arterial pressure (mmHg)	91·0 ±2·6	85·8 ±3·9	100·6 ±4·5	87·7 ±4·1	82·4 ±2·2	76·2 ±2·8*
Mean pulmonary arterial pressure (mmHg)	16·5 ±1·7	11·3 ±1·0*	31·8 ±1·6	23·9 ±2·0*	37·0 ±1·5	24·7 ±1·4
Mean right atrial pressure (mmHg)	5·2 ±1·4	2·8 ±1·2	10·4 ±1·5	7·2 ±1·4*	12·8 ±1·4	8·5 ±1·3*
Left ventricular filling pressure (mmHg)	11·2 ±4·6	6·3 ±1·1*	23·6 ±1·0	15·2 ±1·5*	29·0 ±1·6	18·7 ±1·8*
Cardiac index (l/min per m²)	2·9 ±0·2	2·9 ±0·2	2·6 ±0·1	3·1 ±0·2*	1·8 ±0·1	2·2 ±0·1*
Stroke work index (g m per m²)	38·8 ±7·6	34·5 ±6·2	33·6 ±2·9	34·2 ±1·8	13·8 ±1·1	17·6 ±1·5*
Systemic vascular resistance (dynes s cm⁻⁵)	1383 ±148	1321 ±119	1577 ±141	1231 ±146	1908 ±260	1431 ±137*

All results expressed as mean ±SEM.
C, control; NP, during nitroprusside therapy.
*$P < 0·05$ (nitroprusside v control).
†Chatterjee *et al.* (1973a).

filling pressures, together with a slight to moderate decrease in mean arterial pressure. Cardiac index and stroke volume index, however, increased consistently only in group II and group III patients. Despite a fall in arterial pressure, stroke work index increased in most patients in these two groups. Heart rate also did not change in these patients. In contrast, in patients without left ventricular failure and with normal left ventricular filling pressure (group I), cardiac index did not change and stroke volume and stroke work indices declined, with a reflex increase in heart rate. An increase in stroke volume with a decrease in left ventricular filling pressure, suggesting improved left ventricular performance, was seen in patients in groups II and III, but not in group I (Fig. 2). Decreases in systemic vascular resistance and in systemic and pulmonary venous pressures, in patients receiving nitroprusside infusion, suggest that nitroprusside possesses dilating effects on both precapillary resistance and postcapillary capacitance vascular beds. Miller *et al.* (1975) have suggested that nitroprusside has a relatively balanced effect on these two vascular beds. Absence of an increase in stroke volume in patients with initially normal left ventricular filling pressure is probably related to a move down the ascending limb of the ventricular function curve with a further reduction in end-diastolic volume. Cardiac output and stroke volume may not increase in some patients with high left ventricular filling pressure if this is reduced considerably to a very low level. These observations emphasise the importance of monitoring left ventricular filling pressure, not only to identify those patients likely to derive haemodynamic benefits from nitroprusside infusion, but also to avoid excessive reduction of left ventricular filling pressure.

The haemodynamic effects of intravenous phentolamine in patients with acute myocardial infarction are similar to those of sodium nitroprusside (Kelly *et al.*, 1973; Walinsky *et al.*, 1974; Gould *et al.*, 1974; Perret *et al.*, 1975). Phentolamine, an α-adrenergic blocking agent, also possesses direct smooth muscle relaxing effects. It not only reduces arteriolar tone, but also increases peripheral venous capacitance (Abboud *et al.*, 1968). Phentolamine decreases systemic and pulmonary vascular resistances, and arterial, pulmonary arterial, and left ventricular filling pressures. Right atrial pressure also falls in the majority of patients. In most patients (approximately 90%) with raised left ventricular filling pressure, cardiac output and stroke volume increase. In patients with normal left ventricular filling pressure, however, changes in cardiac output and stroke volume are less consistent. Thus, improved left ventricular performance with phentolamine tends to occur, as with nitroprusside, in patients with high left ventricular filling pressure. One significant difference between the haemodynamic effects of sodium nitroprusside and those of intravenous phentolamine is the tendency to develop tachycardia during phentolamine infusion. In approximately 80 per cent of patients with acute myocardial infarction with either normal or raised left ventricular filling pressures, significant tachycardia occurs during phentolamine infusion (Fig. 3). The mechanism responsible for tachycardia with phentolamine is not clear. Increased synthesis and release of cardiac noradrenaline has been shown to occur in experimental animals (Dairman *et al.*, 1968; Bagwell *et al.*, 1970) and might possibly play a role in phentolamine-induced tachycardia. Phentolamine has also been shown to have indirect inotropic effects in experimental animals (Singh *et al.*, 1970; Zahir and Gould, 1971). From a

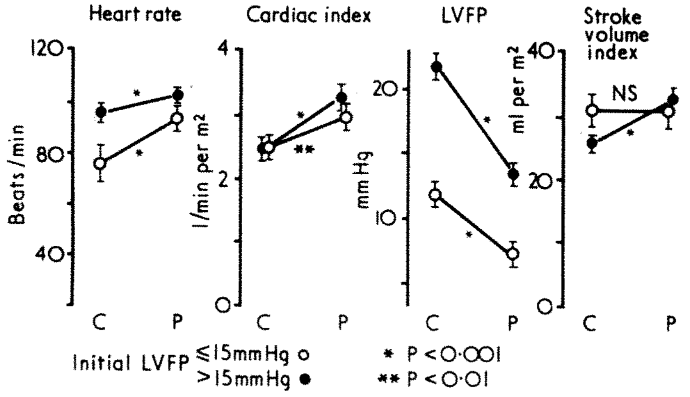

Fig. 3 *The haemodynamic effects of phentolamine in patients with acute myocardial infarction are summarised from the published reports (Kelly* et al., *1973; Walinsky* et al., *1974; Gould* et al., *1974; Perret* et al., *1975). Patients were divided into two groups: those with initial left ventricular filling pressure less than 15 mmHg (○) (14 patients), and those with initial left ventricular filling pressure greater than 15 mmHg (●) (37 patients). Stroke volume increased consistently only in patients with higher left ventricular filling pressure. Heart rate, however, increased in both groups (Chatterjee and Parmley, 1976: reprinted by permission of* Progress in Cardiovascular Diseases*). C = control; P = after phentolamine.*

practical point of view, tachycardia and indirect inotropic effects during phentolamine therapy are distinct disadvantages, because of the possible increase in myocardial oxygen demand which might jeopardise ischaemic myocardium in these patients.

Nitroglycerin, whether administered intravenously or sublingually, and sublingual isosorbide dinitrate, cause a significant decrease in left ventricular filling pressure and right atrial pressure as a result of their dilating effect on the capacitance venous bed. Arteriolar dilatation with nitrites is less and so the decrease in systemic vascular resistance and left ventricular ejection impedance tend to be less than the reduction in preload. Therefore, though there is almost always a decrease in left ventricular filling pressure, there is little or no increase and may even be a decrease in cardiac output and stroke volume. The changes in stroke volume and in left ventricular filling pressure produced by nitroglycerin in patients with acute myocardial infarction (both sublingual and intravenous) are shown in Fig. 4; These haemodynamic data have been collected from published reports (Gold *et al.*, 1972; Williams *et al.*, 1975a; Flaherty *et al.*, 1975; Come *et al.*, 1975; Borer *et al.*, 1975; Armstrong *et al.*, 1975b). It is apparent that there was usually a decrease in stroke volume in patients with a normal left ventricular filling pressure, and when the filling pressure decreased to significantly less than 15 mmHg after nitroglycerin. When left ventricular filling pressure remained above 15 mmHg, stroke volume either remained unchanged or increased, though the magnitude of the increase in stroke volume was usually unimpressive. Heart rate tends to increase when there is a decrease in stroke volume resulting from a pronounced decrease in left ventricular filling pressure.

The haemodynamic effects of these vasodilator agents may provide a rational basis for the choice of a particular agent for a specific therapeutic objective. If the major purpose of treatment is to relieve pulmonary venous congestion in patients who have a persistently raised left ventricular filling pressure, with relatively adequate cardiac output at rest, nitrites might fulfil this objective. On the other hand, if inadequate cardiac output accompanies high left ventricular filling pressure, nitroprusside or phentolamine might be the agents of choice. However, much more clinical experience will be needed to confirm the validity of such a therapeutic approach to the management of pump failure complicating acute myocardial infarction.

Metabolic response to vasodilator treatment in patients with acute myocardial infarction

A potential hazard of vasodilator therapy in patients with obstructive coronary artery disease, with or without recent myocardial infarction, is increased myocardial ischaemia as a result of a reduction in arterial pressure and therefore coronary artery perfusion pressure. Myocardial perfusion however, is dependent not only on the perfusion pressure but also on the resistance of the distal coronary artery bed and transmyocardial pressure gradient (Fortuin *et al.*, 1971). Furthermore, concomitant changes in the determinants of myocardial oxygen requirement will influence myocardial ischaemia by changing the ratio of oxygen supply to demand. Myocardial metabolism during vaso-

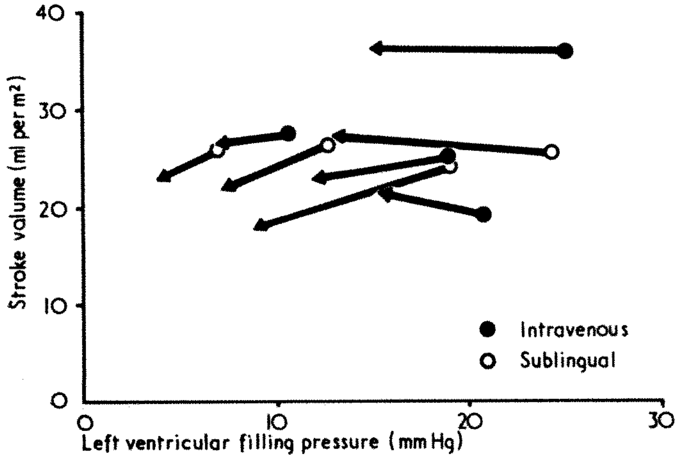

Fig. 4 *Haemodynamic effects of intravenous (45 patients) and sublingual nitroglycerin (28 patients) in acute myocardial infarction. Data collected from published reports (Flaherty* et al., *1975; Come* et al., *1975; Borer* et al., *1975; Armstrong* et al., *1975a, b; Williams* et al., *1975b). Patients were divided into those with high initial filling pressure (more than 15 mmHg) and those with low initial filling pressure, and the former were further subdivided into those in whom filling pressure fell significantly and those in whom it did not. It is apparent that the predominant effect of nitroglycerin was to reduce left ventricular filling pressure, though stroke volume increased slightly in some patients with initially high filling pressure.*

dilator therapy will depend on these various opposing factors which might alter both myocardial perfusion and the determinants of myocardial oxygen demand.

In experimental animals with patent coronary arteries, sodium nitroprusside decreases coronary vascular resistance and increases coronary blood flow (Rowe and Henderson, 1974). But in patients with acute myocardial infarction complicated by left ventricular failure, coronary sinus blood flow, an approximate measure of coronary blood flow, myocardial oxygen extraction, and consumption all tend to decrease during vasodilator treatment (Chatterjee *et al.*, 1973a). This is consistent with the fact that the major determinants of myocardial oxygen demand either remain unchanged or fall: left ventricular systolic and end diastolic pressures decrease, while heart rate and myocardial contractility are unaffected. There was no change in myocardial lactate extraction during vasodilator therapy, indicating that there was no increase in myocardial ischaemia in these patients.

Intravenous phentolamine increases overall myocardial blood flow in patients with acute myocardial infarction, despite a fall in blood pressure (Gould *et al.*, 1975). However, this increase in coronary blood flow may be partly the result of an increase in myocardial oxygen demand, as a result of tachycardia.

Although the metabolic effects of nitroglycerin have been investigated in patients with chronic ischaemic heart disease (Brachfeld *et al.*, 1959; Gorlin *et al.*, 1959; Frohlich and Scott, 1962; Luebs *et al.*, 1966; Ganz and Marcus, 1972), little is known about changes in myocardial metabolism after nitroglycerin in patients with acute myocardial infarction. When there is left ventricular failure, nitroglycerin, like nitroprusside, decreases left ventricular systolic and end diastolic pressures without any significant change in heart rate or contractility. It is likely, therefore, that overall myocardial oxygen demand and blood flow would decrease in such patients during nitroglycerin treatment. Thus, the overall myocardial oxygen supply/demand ratio and myocardial metabolism might improve. But an excessive reduction in arterial pressure, irrespective of the vasodilator used, might, by reducing coronary blood flow, aggravate myocardial hypoxia. Furthermore, even with a moderate reduction in arterial pressure, there is a possibility of increased hypoxia in some areas of the myocardium as a result of the reduction in perfusion pressure during vasodilator treatment. It would be useful to be able to measure regional metabolism, to determine the degree of reduction of arterial pressure that could be tolerated, but in clinical practice this is not possible at the present time.

In experimental models, investigations of changes in regional metabolism of ischaemic myocardial segments during vasodilator treatment have produced conflicting results. Some authors have reported improvement in regional myocardial metabolism and mechanical function during nitroprusside infusion (Cohn *et al.*, 1974a; Mueller *et al.*, 1974; Da Luz *et al.*, 1975; Ramanathan *et al.*, 1975) and others deterioration or no change (Kerber and Abboud, 1975; Kerber *et al.*, 1976; Chiariello *et al.*, 1976). Similarly, there have been contradictory and conflicting reports on the effects of nitroglycerin on the extent of myocardial ischaemic injury, as judged by changes in the magnitude of ST segment elevation after acute myocardial infarction. Decrease in ST segment elevation suggesting reduction of the extent of myocardial ischaemic injury has been observed during nitroglycerin therapy (Borer *et al.*, 1975; Come *et al.*, 1975; Flaherty *et al.*, 1975; Chiariello *et al.*, 1976). However, no change or even an increase in ST segment elevation has been reported by Lang *et al.* (1976). Furthermore, a paradoxical adverse effect of nitroglycerin on segmental left ventricular wall motion has also been reported in patients with obstructive coronary artery disease and 'coronary steal' has been suggested as the underlying mechanism (Codini *et al.*, 1976). Fam and McGregor (1964) have previously suggested that a 'coronary steal syndrome' might occur with nitroglycerin where there is a large proximal resistance within diseased coronary arteries. This 'coronary steal' from ischaemic myocardium may also occur with nitroprusside or phentolamine and result in increased ischaemia (Chiariello *et al.*, 1976; Brown. *et al.*, 1976; Farnham *et al.*, 1976; Engler *et al.*, 1976).

These limited experimental and clinical investigations suggest that, irrespective of the vasodilator agent used, the effects of vasodilator treatment on the metabolic and mechanical function of ischaemic myocardium are likely to be variable, being determined by concurrent changes in the various factors that influence myocardial perfusion and oxygen demand. Furthermore, extrapolation of the results of experimental studies to the treatment of patients is difficult and should be done with extreme caution. Not only is coronary anatomy different in experimental animals, but the experimental design may be far removed from actual clinical situations. For example, the effects of vasodilators on regional myocardial metabolism and on the extent of myocardial ischaemic injury have been studied in experimental animals within a few minutes of acute coronary artery occlusion, whereas most patients with acute myocardial infarction are treated several hours or days after the onset. In addition, most experimental studies have been performed in animals without heart failure, while vasodilator treatment is most useful haemodynamically in patients with significant pump failure. Thus, the effects of vasodilator treatment on relatively ischaemic or hypoxic myocardial segments in patients with obstructive coronary artery disease remain uncertain. But it should be emphasised that in clinical practice a large reduction in arterial pressure, particularly in hypotensive or normotensive patients, whichever vasodilator agent is used, should be avoided since this may aggravate existing myocardial ischaemia. Fortunately, when the objective of treatment is to improve pump function, the beneficial haemodynamic effects of vasodilator treatment can be obtained in many patients without a significant reduction in arterial pressure (Chatterjee *et al.*, 1973a).

Table 2 *Clinical data in 43 patients with severe pump failure complicating acute myocardial infarction treated with intravenous vasodilators**

Clinical data	*No. of patients*
Site of infarct	
Anterior	26
Inferior	10
Combined	3
Posterior	1
Subendocardial	1
Left bundle-branch block	2
Previous infarct	30
Cardiomegaly	31
Pulmonary oedema	43
Shock	17
Complications of treatment	
Sudden hypotension	3
Nausea	4
Mental confusion	3
Hiccough	9

*Chatterjee *et al.*, 1976c.

Influence of vasodilator treatment on prognosis of pump failure complicating acute myocardial infarction

In recent years, as hospital mortality from primary arrhythmias has strikingly decreased, pump failure has emerged as the primary cause of death in patients with acute myocardial infarction. It has also become apparent that the mortality from pump failure is directly proportional to the severity of depression of cardiac function. Thus, the hospital mortality with conventional therapy is 30 to 40 per cent in patients with frank pulmonary oedema, and approaches 100 per cent when the clinical features of cardiogenic shock are present (Killip and Kimball, 1967; Swan *et al.*, 1970; Wolk *et al.*, 1972; Scheidt *et al.*, 1973; Weber *et al.*, 1973). With the advent of safe bedside monitoring, prognostic indices based on haemodynamic data have become available. Whether overt clinical manifestations of pump failure are present or not, certain haemodynamic measurements provide a sensitive means of evaluating the immediate prognosis of such patients. In patients with a stroke work index of 20 g m per m^2 or less and a left ventricular filling pressure of 15 mmHg or more, the hospital mortality with conventional therapy approaches 80 per cent (Chatterjee and Swan, 1973). Whether such a grim outlook in these patients is influenced favourably by vasodilator treatment cannot be determined with certainty without a matched control series. However, recent investigations suggest that intravenous vasodilator treatment with careful haemodynamic monitoring might improve the immediate prognosis in patients with severe pump failure complicating acute myocardial infarction (Chatterjee *et al.*, 1976c). Forty-three patients with severe pump failure were treated with nitroprusside (40 patients) or phentolamine (3 patients); clinical data including complications of vasodilator therapy are summarised in Table 2. Not only clinically, but also on the basis of initial haemodynamic observations

Table 3 *Haemodynamic changes during intravenous vasodilator therapy in 43 patients with severe pump failure complicating acute myocardial infarction**

	Control	*Vasodilator*	*P*
Heart rate (beats/min)	100 ± 2·4	99 ± 2·7	NS
Arterial mean pressure (mmHg)	83 ± 1·5	73 ± 1·7	< 0·0005
Pulmonary arterial mean pressure (mmHg)	39 ± 1·2	28 ± 1·1	< 0·0005
Right atrial mean pressure (mmHg)	13 ± 0·8	9 ± 0·6	< 0·0005
Left ventricular filling pressure (mmHg)	31 ± 1·0	20 ± 0·8	< 0·0005
Cardiac index (l/min per m^2)	1·7 ± 0·05	2·2 ± 0·06	< 0·0005
Stroke volume index (ml per m^2)	17·3 ± 0·2	22·8 ± 0·8	< 0·0005
Stroke work index (g m per m^2)	14 ± 0·7	19 ± 0·9	< 0·005
Systemic vascular resistance (dynes s cm^{-5})	2023 ± 112	1435 ± 65	< 0·0005

All results expressed as mean ± SEM.
Chatterjee *et al.* (1976c).

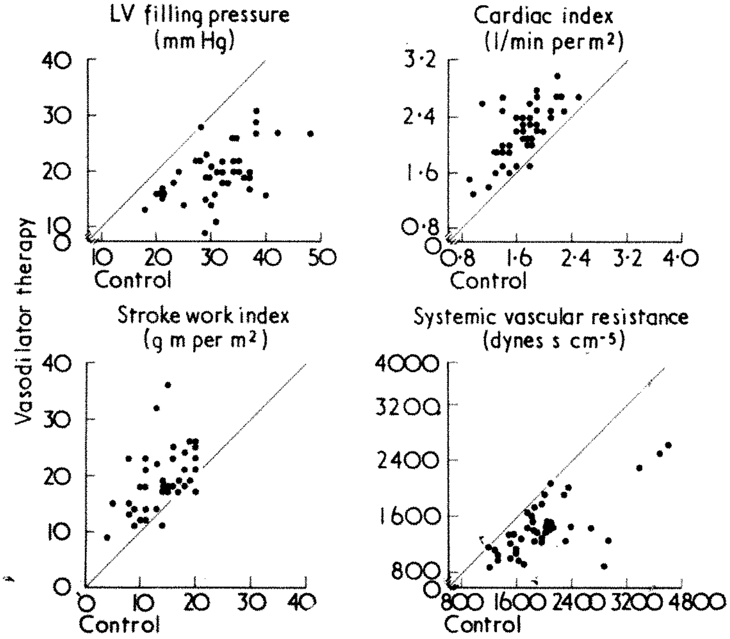

Fig. 5 *Changes in left ventricular filling pressure, cardiac index, stroke work index, and systemic vascular resistance during intravenous vasodilator treatment in 43 patients with severe pump failure complicating acute myocardial infarction. In almost all patients haemodynamic improvement was observed (Chatterjee* et al., *1976c: reprinted by permission of* Circulation*).*

(stroke work index less than 20 g m per m^2 and left ventricular filling pressure more than 15 mmHg), these patients had severe depression of cardiac function. Haemodynamic changes during intravenous vasodilator treatment are summarised in Table 3. A beneficial haemodynamic response was observed in almost all patients. Cardiac output increased while pulmonary artery wedge pressure decreased (Fig. 5). Despite this initial favourable haemodynamic response, 19 patients (44%) died in the hospital, 15 with uncontrolled failure. Thus, hospital mortality caused by pump failure was 34 per cent. Most studies indicate that in the presence of severe haemodynamic depression, the hospital mortality with conventional treatment exceeds 75 per cent. With vasodilator treatment in patients with similar haemodynamic findings, mortality was about 50 per cent (Table 4). However, when the stroke work index is extremely low (less than 10 g m per m^2) and left ventricular filling pressure is raised, the immediate prognosis remains very bad. Eleven of the 43 patients had a stroke work index less than 10 g m per m^2; of these only 2 survived, giving a hospital mortality of 82 per cent. Thus, it appears that vasodilator treatment is most likely to be effective in patients with an initial stroke work index greater than 10 g m per m^2 and raised left ventricular filling pressure.

Although these findings suggest an improvement in the initial prognosis of patients with severe pump failure using vasodilator treatment, the late prognosis was unfavourable in the survivors. Sixty-two per cent of the survivors died within 1 to 25 months (average 9·2 months) after discharge, and 71 per cent

Table 4 *Comparison of mortality rates with conventional and vasodilator treatment in power failure after acute myocardial infarction*

Authors	*No. of patients*	*CI (l/min per m^2)*	*SWI (g m per m^2)*	*LVFP (mmHg)*	*CWI (kg m per m^2)*	*SWI/LVFP*	*Per cent mortality*	
							Conventional	*Vasodilator*
Ratshin *et al.* (1972)	11	2·3	—	15	—	—	100	53
Scheidt *et al.* (1973)	29	—	20	—	—	—	72	44
Scheidt *et al.* (1973)	29	—	—	—	1·75	—	76	50
Bleifeld *et al.* (1974)	42	—	—	—	—	1·2	80	44
Chatterjee *et al.* (1973a, 1976c)	15	—	20	15	—	—	80	44

CI, cardiac index; SWI, stroke work index; LVFP, left ventricular filling pressure; CWI, cardiac work index.

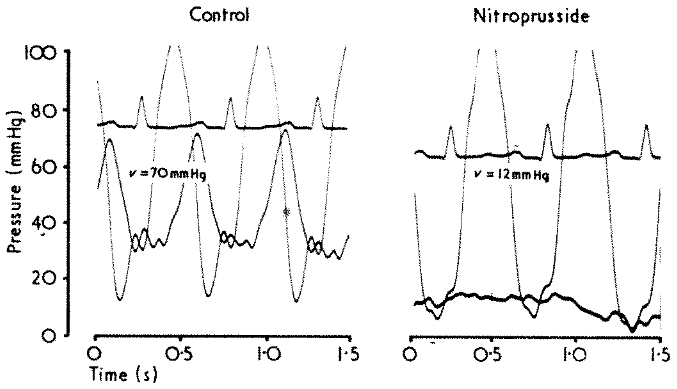

Fig. 6 *Simultaneously recorded left ventricular pressure and pulmonary artery wedge pressure before and 25 minutes later during nitroprusside infusion in a patient with severe mitral regurgitation. A distinct decrease in pulmonary artery wedge mean pressure, the height of the* v *wave, and in left ventricular end diastolic pressure was seen during nitroprusside infusion (Chatterjee* et al., *1973b: reprinted by permission of* Circulation*).*

died of uncontrolled pump failure. Furthermore, about 50 per cent of the survivors remained in severe pump failure. It is apparent that the long-term prognosis in these patients remains bad.

Vasodilator treatment for valvular regurgitation

MITRAL REGURGITATION

As an increase in impedance to left ventricular ejection increases mitral regurgitation (Braunwald *et al.*, 1957), it is not surprising that vasodilator agents can produce beneficial haemodynamic effects in patients with mitral regurgitation (Chatterjee *et al.*, 1973b; Goodman *et al.*, 1974; Sniderman *et al.*, 1974; Harshaw *et al.*, 1975). The haemodynamic effects of intravenous sodium nitroprusside infusion are a decrease in systemic and pulmonary vascular resistance, and a decrease in pulmonary artery wedge, right atrial, and pulmonary artery pressures. Left ventricular forward stroke volume and cardiac output increases and usually there is no significant change in heart rate (Table 5). Reduction in the regurgitant volume during nitroprusside infusion is indicated by a distinct decrease in the amplitude of the peak *v* wave in the pulmonary artery wedge pressure (Fig. 6). Indeed, the calculated regurgitant volume decreases considerably during nitroprusside infusion, with a concomitant increase in forward stroke volume and little change in the total stroke volume (Fig. 7). This redistribution of the total stroke volume of the left ventricle, with more blood ejected forwards into the aorta and less backwards into the left atrium, accounts for the distinct haemodynamic improvement in these patients. Since the left ventricle operates at a lower filling pressure and end diastolic volume, the calculated ejection fraction usually increases. The decrease in the regurgitant volume, however, may not be entirely the result of the reduction of impedance to left ventricular ejection. Decreased left ventricular chamber size and improved functional integrity of the mitral valve apparatus may play a significant role.

Intravenous phentolamine and nitroglycerin (sublingual or topical) produce haemodynamic effects that are very similar to those of nitroprusside. With nitroglycerin, however, forward stroke volume

Table 5 *Haemodynamic effects of nitroprusside in 8 patients with mitral regurgitation**

	Control	*Nitroprusside*	*P*
Heart rate (beats/min)	101 ±5·9	95 ±4·9	<0·01
Arterial mean pressure (mmHg)	83 ±3·8	70 ±3·3	<0·005
Pulmonary arterial mean pressure (mmHg)	45 ±2·4	29 ±2·4	<0·0005
Pulmonary artery mean wedge pressure (mmHg)	33 ±1·8	16 ±1·4	<0·0005
Pulmonary artery wedge pressure *v* wave (mmHg)	50 ±4·5	19 ±2·9	<0·0005
Cardiac index (l/min per m^2)	2·2 ±0·35	3·3 ±0·47	<0·005
Forward stroke volume index (ml per m^2)	23 ±4·4	36 ±6·6	<0·005
Stroke work index (g m per m^2)	16 ±3	29 ±6	<0·01
Systemic vascular resistance (dynes s cm^{-5})	1802 ±331	1102 ±241	<0·005
Pulmonary vascular resistance (dynes s cm^{-5})	263 ±45	163 ±26	<0·025

All results expressed as mean ±SEM.
*Chatterjee *et al.* (1973b).

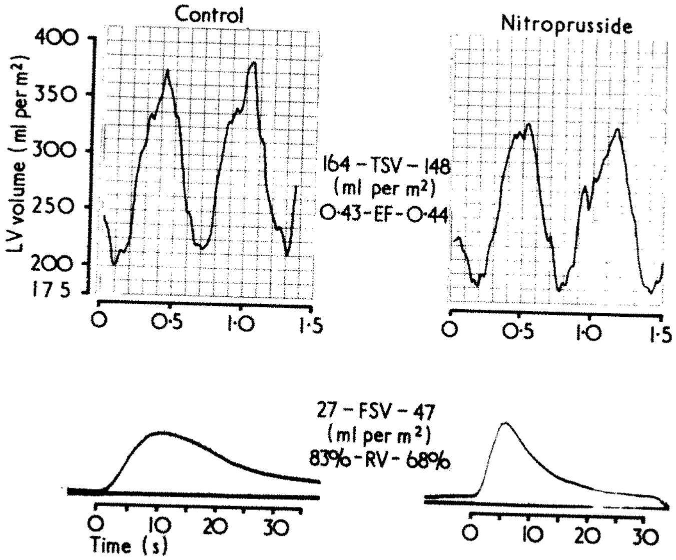

Fig. 7 *Changes in the regurgitant volume during nitroprusside infusion in a patient with severe mitral regurgitation. Regurgitant volume (RV) was calculated by subtracting the forward stroke volume (FSV) obtained from the dye concentration curves (lower panels) from the total left ventricular stroke volume (TSV) calculated from the left ventricular volume curves (upper panels) obtained from left ventriculograms in right anterior oblique projection, and was expressed as a percentage of the total stroke volume. RV decreased significantly during nitroprusside infusion. Ejection fraction (EF) is unchanged. (Chatterjee* et al., *1973b: reprinted by permission of* Circulation*).*

may not increase, in spite of a decrease in regurgitant volume. This may result from the striking reduction in end diastolic volume, related to the greater effect of nitroglycerin on ventricular preload than on afterload.

AORTIC REGURGITATION

It has been recognised clinically for a long time that inhalation of amyl nitrite, a vasodilator, decreases the duration and intensity of the Austin-Flint murmur in patients with aortic regurgitation, indicating a reduction in regurgitant volume. Indeed, the administration of amyl nitrite results in a decrease in arterial pressure and left ventricular end diastolic pressure, together with an increase in effective stroke volume (Delius and Enghoff, 1970). Similar beneficial haemodynamic effects of sodium nitroprusside are seen particularly in those patients with a raised left ventricular end diastolic pressure and reduced ejection fraction. Determination of instantaneous changes in pressure and flow in the aortic root during nitroprusside infusion show that there is a significant reduction in aortic impedance which might account for the increase in forward stroke volume and reduction of regurgitant fraction in patients with aortic regurgitation (Pepine *et al.*, 1976; Bolen and Alderman, 1976). There is usually, however, a slight to moderate decrease in arterial pressure. Therefore, in patients with aortic regurgitation and associated obstructive coronary artery disease, vasodilators should be used cautiously, because a further reduction of an already reduced aortic diastolic pressure may impair myocardial perfusion.

Since vasodilator treatment may improve the haemodynamic state of patients with mitral or aortic regurgitation, it can be applied with advantage in certain clinical situations. In patients with acute mitral regurgitation complicating myocardial infarction, it may be possible to defer a hazardous surgical operation (Fig. 8). Similarly, when acute aortic regurgitation with cardiac failure complicates bacterial endocarditis, there is a potential role for vasodilator treatment to tide the patients over a critical period until the infection is under control. When surgical treatment is contraindicated in patients with chronic mitral or aortic regurgitation, the addition of vasodilators to conventional antifailure treatment may produce significant haemodynamic and clinical improvement. It is also possible that the smaller left ventricular volume, reduced regurgitant fraction, and decreased left ventricular work that results from vasodilator treatment may be helpful in delaying the progressive ventricular dysfunction that occurs in patients with severe mitral or aortic regurgitation. Without further experience, however, the efficacy of vasodilator treatment for long-term management of patients with valvar regurgitation remains conjectural.

Vasodilator treatment for chronic congestive heart failure

Congestive heart failure, irrespective of the aetiology, not uncommonly becomes refractory to conventional therapy with digitalis and diuretics. The haemodynamic effects of intravenous sodium

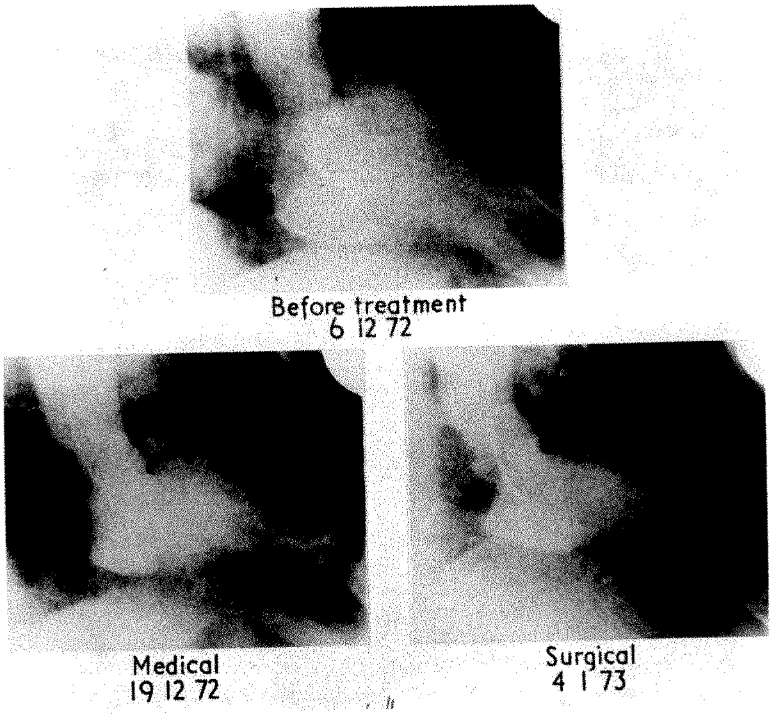

Fig. 8 *End systolic frames from left ventriculograms in right anterior oblique projection in a patient with severe mitral regurgitation as a reuslt of papillary muscle dysfunction complicating acute myocardial infarction. Before vasodilator treatment, important mitral regurgitation was shown by dense opacification of the left atrium during left ventriculograms (6.12.72). During vasodilator treatment left ventriculograms showed an obvious reduction in severity of mitral regurgitation 19.12.72). The patient was maintained on vasodilator treatment until operation was performed. The postoperative study (4.1.73) showed no significant mitral regurgitation.*

nitroprusside in patients with chronic congestive heart failure are similar to those observed in patients with acute heart failure (Cohn *et al.*, 1974b; Guiha *et al.*, 1974; Chatterjee, 1975; Miller *et al.*, 1975; Chatterjee *et al.*, 1976a; Chatterjee and Parmley, 1976). With an adequate dose, cardiac output and stroke volume increase, with decreases in systemic vascular resistance, and in mean arterial and pulmonary artery pressures. Peripheral venous capacitance also increases with a decrease in right atrial and pulmonary artery wedge pressures (Fig. 9). This favourable haemodynamic response is usually accompanied by clinical improvement. Intravenous phentolamine produces similar haemodynamic effects (Gould *et al.*, 1969; Majid *et al.*, 1971; Williams *et al.*, 1975b). These haemodynamic effects of nitroprusside or phentolamine are quickly reversed when intravenous treatment is discontinued. Intravenous treatment is thus clinically applicable only for the short-term management of patients with chronic congestive heart failure or to determine the magnitude of the haemodynamic response before starting nonparenteral vasodilator treatment.

Several nonparenteral vasodilators have been investigated for the long-term management of heart failure. Sublingual nitroglycerin (Gold *et al.*, 1972) usually decreases pulmonary and systemic venous pressures. Cardiac output may or may not increase. Clinically, therefore, sublingual nitroglycerin can be used effectively for the treatment of acute pulmonary oedema. The duration of action of sublingual nitroglycerin is extremely short, not exceeding 30 minutes; thus its clinical use in the long-term management of heart failure is limited.

The haemodynamic effects of nitroglycerin ointment, which are similar to those of the sublingual form, last approximately 3 to 5 hours (Taylor *et al.*, 1975). Though there is usually a significant reduction in systemic and pulmonary venous pressures, the increase in cardiac output is usually only slight. In some patients with severe heart failure there may be no haemodynamic changes (Chatterjee *et al.*, 1976a), perhaps because of lack of absorption. Furthermore, the effective dose for an individual patient cannot be predicted without haemodynamic measurements.

Sublingual isosorbide dinitrate, in a dose of 2·5 to 15 mg, decreases systemic and pulmonary venous pressure, as a result of an increase in peripheral venous capacitance. Cardiac output increases slightly along with a decrease in arterial pressure (Gray *et al.*, 1975). The haemodynamic and peripheral vascular effects of isosorbide dinitrate

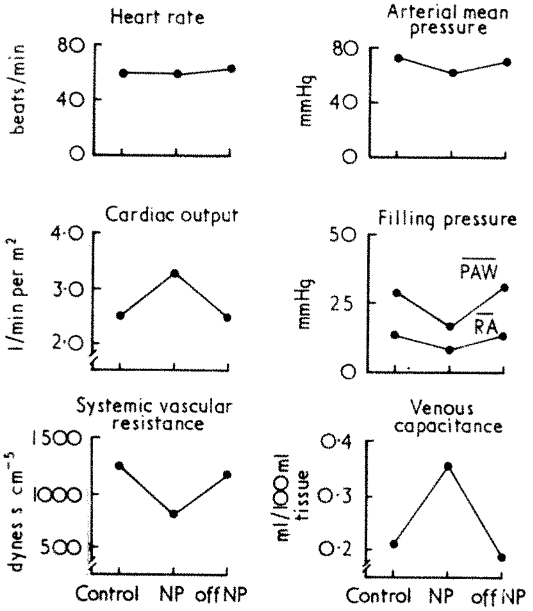

Fig. 9 *Effect of intravenous nitroprusside (NP) infusion on peripheral vascular and central haemodynamic changes in a patient with severe chronic congestive heart failure. Pulmonary arterial wedge pressure and right atrial pressure decreased with an increase in venous capacitance. Cardiac output increased with a decrease in systemic vascular resistance. Mean arterial pressure decreased only slightly and the heart rate did not change. Haemodynamic values returned almost to control level after stopping nitroprusside infusion.*

become evident within 15 minutes and are maximal between 15 and 45 minutes, but last for approximately 90 minutes (Fig. 10). Frequent administration is therefore necessary. Oral isosorbide dinitrate in a dose of 20 to 40 mg may cause a significant decrease in pulmonary venous pressures for 3 to 4 hours in some patients with chronic congestive heart failure, though its effect on cardiac output is unknown (Franciosa *et al.*, 1974). Chewable isosorbide dinitrate also appears to be effective in reducing pulmonary and systemic venous pressures (Mikulic *et al.*, 1975). From the clinical experience reported so far, it appears that most nitrite preparations can produce a significant reduction in pulmonary and systemic venous pressures and so are useful for the relief of pulmonary and systemic venous congestion. As the increase in cardiac output is no more than slight, nitrites may be less effective in those patients with left ventricular failure in whom a low cardiac output is the primary problem. A vasodilator agent with a predominant effect on the precapillary resistance bed may produce a greater increase in cardiac output and therefore be more useful.

Preliminary experience with oral hydrallazine, a predominantly arteriolar dilator, in patients with refractory heart failure has shown that it can produce a sustained increase in cardiac output and stroke volume (Chatterjee *et al.*, 1976b; Franciosa and Cohn, 1976), together with a significant reduction in systemic vascular resistance. When hydrallazine was administered in a dose of 50 to 75 mg every 6 hours, no consistent changes in systemic and pulmonary venous pressures, arterial pressure, or heart rate were observed (Table 6). It is not clear why there was no change in heart rate in these patients: a relatively minor reduction in arterial pressure or possibly a sluggish baroreceptor response in patients with chronic heart failure might be responsible. The absence of a significant reduction in arterial pressure in normotensive patients may be an advantage of this drug in the management of patients with heart failure caused by ischaemic heart disease, since coronary artery perfusion pressure would be maintained. On the other hand, systemic and pulmonary venous pressures may remain high and weight gain resulting from an increase in extracellular and plasma volume may occur despite an increase in cardiac output during treatment with oral hydrallazine. The

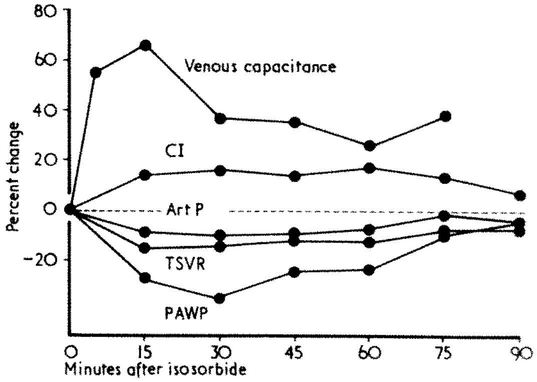

Fig. 10 *Haemodynamic effects of sublingual isosorbide dinitrate in patients with chronic congestive heart failure. These data represent the mean percentage change from control values in 12 patients. There was an increase in cardiac index (CI), stroke volume, and venous capacitance, and a decrease in systemic vascular resistance (TSVR), pulmonary arterial wedge pressure (PAWP), and arterial pressure (Art P), lasting about 90 minutes (Gray* et al., *1975: reprinted by permission of* American Heart Journal*).*

Table 6 *Haemodynamic effects of oral hydrallazine in 10 patients with refractory heart failure**

	Control	*Hydrallazine*	*P*
Heart rate (beats/min)	90 ±6·9	90 ±5·8	NS
Arterial mean pressure (mmHg)	89 ±4·5	85 ±4·0	NS
Pulmonary arterial mean pressure (mmHg)	37 ±3·4	38 ±3·1	NS
Left ventricular filling pressure (mmHg)	24 ±2·0	23 ±2·1	NS
Cardiac index (l/min per m^2)	1·99 ±0·15	3·39 ±0·29	$<0·001$
Stroke volume index (ml per m^2)	23 ±3·0	38 ±3·5	$<0·001$
Stroke work index (g m per m^2)	23 ±2·4	36 ±3·7	$<0·001$
Systemic vascular resistance (dynes s cm^{-5})	1748 ±129	998 ±115	$<0·001$
Pulmonary vascular resistance (dynes s cm^{-5})	328 ±54	203 ±32	$<0·001$

NS = not significant.
*Chatterjee *et al.* (1976b).

addition of diuretics and nitrites is therefore necessary.

Complications

Unexpected hypotension is the most serious complication of intravenous vasodilator treatment and may be hazardous for patients with acute myocardial infarction and pump failure, but is usually reversed within 5 to 10 minutes after stopping intravenous treatment. To avoid hypotension sodium nitroprusside or phentolamine should be started in a very low dose (nitroprusside 16 to 20 μg per min, phentolamine 0·1 to 0·2 mg per min); the subsequent increase in dose should also be gradual. Careful monitoring of changes in cardiac output, systemic vascular resistance, and filling pressures is necessary. The maximum dose of vasodilator needs to be determined for each individual patient. Nitroprusside has been used without adverse effects in doses up to 430 μg per min, and phentolamine in doses up to 2 mg per min in patients with acute heart failure. Mental confusion, involuntary muscular twitchings, convulsions, nausea, vomiting, and hiccough are other complications of intravenous vasodilator treatment. Methaemoglobinaemia, hypothyroidism, and cyanide poisoning are rare but serious potential complications of nitroprusside treatment. In patients needing prolonged nitroprusside treatment, blood thiocyanate level should be monitored, particularly in the presence of hepatic and renal failure which retard the metabolism of nitroprusside: the toxic level of thiocyanate is about 12 mg/dl.

The nonparenteral vasodilators sublingual nitroglycerin and isosorbide dinitrate may produce severe unexpected hypotension. Headache, nausea, and postural hypotension are potential problems of nitrate therapy. Limited experience in patients with chronic heart failure has shown that oral hydrallazine in doses of 50 to 75 mg every 6 hours does not produce postural hypotension. Nausea and abdominal discomfort are usually transient complications of hydrallazine treatment. Central nervous system complications, skin eruption, peripheral neuropathy, and the systemic lupus erythematosus syndrome are more serious complications of continued hydrallazine treatment; the risks increase when the daily dose exceeds 400 mg. Long-term follow-up and further experience will be needed to determine the incidence of these complications in patients with heart failure receiving hydrallazine; without this experience the feasibility of hydrallazine treatment for the long term management of heart failure remains uncertain.

References

Abboud, F. M., Schmid, P. G., and Eckstein, J. W. (1968). Vascular responses after alpha-adrenergic receptor blockade. I. Responses of capacitance and resistance vessels to norepinephrine in man. *Journal of Clinical Investigation*, **47**, 1–9.

Armstrong, P. W., Mathew, M. T., Boroomand, K., and Parker, J. O. (1975a). Hemodynamic effects of nitroglycerin ointment in acute myocardial infarction. *Circulation*, **51** and **52**, Suppl. II, 152.

Armstrong, P. W., Walker, D. C., Burton, J. R., and Parker, J. O. (1975b). Vasodilator therapy in acute myocardial infarction. A comparison of sodium nitroprusside and nitroglycerin. *Circulation*, **52**, 1118–1122.

Bagwell, E. E., Hilliard, C. C., Daniell, H. B., Taylor, P. L., and Walton, R. P. (1970). Studies on the inotropic mechanism of phentolamine. *American Journal of Cardiology*, **25**, 83.

Bleifeld, W., Hanrath, P., Mathey, D., and Merx, W. (1974). Acute myocardial infarction. V. Left and right ventricular haemodynamics in cardiogenic shock. *British Heart Journal*, **36**, 822–834.

Bolen, J. L., and Alderman, E. L. (1976). Hemodynamic consequences of afterload reduction in patients with chronic aortic regurgitation. *Circulation*, **53**, 879–883.

Borer, J. S., Redwood, D. R., Levitt, B., Cagin, N., Bianchi, C., Vallin, H., and Epstein, S. E. (1975). Reduction in myocardial ischaemia with nitroglycerin or nitroglycerin plus phenylephrine administered during acute myocardial infarction. *New England Journal of Medicine*, **293**, 1008–1012.

Brachfeld, N., Bozer, J., and Gorlin, R. (1959). Action of nitroglycerin on the coronary circulation in normal and in mild cardiac subjects. *Circulation*, **19**, 697–704.

Braunwald, E., Welch, G. H., and Sarnoff, S. J. (1957). Hemodynamic effects of quantitatively varied experimental mitral regurgitation. *Circulation Research,* **5,** 539–545.

Brown, T. M., Matthews, O. P., and Walter, P. F. (1976). Assessment of the effect of vasodilator therapy upon hemodynamics and ischemic injury in acute myocardial infarction. *American Journal of Cardiology*, **37,** 123.

Chatterjee, K. (1975). Vasodilator therapy for heart failure. *Annals of Internal Medicine,* **83,** 421–423.

Chatterjee, K., Drew, D., Parmley, W. W., Klausner, S. C., Polansky, J., and Zacherle, B. (1976a). Combination vasodilator therapy for severe chronic congestive heart failure. *Annals of Internal Medicine.*

Chatterjee, K., and Parmley, W. W. (1976). The role of vasodilator therapy in heart failure. *Progress in Cardiovascular Diseases,* **19,** 301–325.

Chatterjee, K., Parmley, W. W., Ganz, W., Forrester, J., Walinsky, P., Crexells, C., and Swan, H. J. C. (1973a). Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. *Circulation,* **48,** 1183–1193.

Chatterjee, K., Parmley, W. W., Massie, B., Greenberg, B., Werner, J., Klausner, S., and Norman, A. (1976b). Oral hydralazine therapy for chronic refractory heart failure. *Circulation,* **54,** 879–883.

Chatterjee, K., Parmley, W. W., Swan, H. J. C., Berman, G., Forrester, J., and Marcus, H. S. (1973b). Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvar apparatus. *Circulation,* **48,** 684–690.

Chatterjee, K., and Swan, H. J. C. (1973). Hemodynamic profile in acute myocardial infarction. In *Myocardial Infarction,* p. 51. Ed. by E. Corday and H. J. C. Swan. Williams and Wilkins, Baltimore.

Chatterjee, K., and Swan, H. J. C. (1974). Vasodilator therapy in acute myocardial infarction. *Modern Concepts of Cardiovascular Disease,* **43,** 119–124.

Chatterjee, K., Swan, H. J. C., Kaushik, V. S., Jobin, G., Magnusson, P., and Forrester, J. S. (1976c). Effects of vasodilator therapy for severe pump failure in acute myocardial infarction on short term and late prognosis. *Circulation,* **53,** 797–802.

Chiariello, M., Gold, H. K., Leinbach, R. C., Davis, M. A., and Maroko, P. R. (1976). Comparison between the effects of nitroglycerin and nitroprusside on ischemic injury during acute myocardial infarction (abstract). *American Journal of Cardiology,* **37,** 127.

Codini, M. A., Bardfeld, P. A., and Spindola-Franco, H. (1976). Paradoxical effect of nitroglycerin on left ventricular wall motion in coronary artery disease. *American Journal of Cardiology,* **37,** 127.

Cohn, J. N., Franciosa, J. A., and Notargiacomo, A. (1974a). Nitroprusside and dobutamine effect on myocardial oxygen supply/demand in experimental myocardial infarction. *Circulation,* **49** and **50,** Suppl. III, 103.

Cohn, J. N., Mathew, K. J., Franciosa, J. A., and Snow, J. A. (1974b). Chronic vasodilator therapy in the management of cardiogenic shock and intractable left ventricular failure. *Annals of Internal Medicine,* **81,** 777–780.

Come, P. C., Flaherty, J. T., Baird, M. C., Rouleau, J. R., Weisfeldt, M. L., Greene, H. L., Becker, L., and Pitt, B. (1975). Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction. *New England Journal of Medicine,* **293,** 1003–1007.

Dairman, W., Gordon, R., Spector, S., Sjoerdsma, A., and Udenfriend, S. (1968). Effect of α-blockers on catecholamine biosynthesis. *Federation Proceedings,* **27,** 240.

Da Luz, P. L., Forrester, J. S., Wyatt, H. L., Tyberg, J. V., Chagrasulis, R., Parmley, W. W., and Swan, H. J. C. (1975). Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium. *Circulation,* **52,** 400–407.

Delius, W., and Enghoff, E. (1970). Studies of the central and peripheral hemodynamic effects of amyl nitrite in patients with aortic insufficiency. *Circulation,* **42,** 787–796.

Engler, R. L., Pearlman, A. S., Goldstein, R. A., Kent, K. M., and Epstein, S. E. (1976). Relative effects of nitroprusside and nitroglycerin on ischemia after experimental coronary occlusion. *Clinical Research,* **24,** 216A.

Fam, W. M., and McGregor, M. (1964). Effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischaemia. *Circulation Research,* **15,** 355–365.

Farnham, D. J., Shah, P. M., Logan, D. C., and Schreiner, B. F. (1976). Nitroprusside ventriculogram: impairment of asynergy. *American Journal of Cardiology,* **37,** 135.

Flaherty, J. T., Reid, P. R., Kelly, D. T., Taylor, D. R., Weisfeldt, M. L., and Pitt, B. (1975). Intravenous nitroglycerin in acute myocardial infarction. *Circulation,* **51,** 132–139.

Fortuin, N. J., Kaihara, S., Becker, L. C., and Pitt, B. (1971). Regional myocardial blood flow in the dog studied with radioactive microspheres. *Cardiovascular Research,* **5,** 331–336.

Franciosa, J. A., and Cohn, J. N. (1976). Hemodynamic improvement with hydralazine in left heart failure. *Clinical Research,* **24,** 217A.

Franciosa, J. A., Guiha, N. H., Limas, C. J. Rodriguera, E., and Cohn, J. N. (1972). Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet,* **1,** 650–654.

Franciosa, J. A., Mikulic, E., Cohn, J. N., Jose, E., and Fabie, A. (1974). Hemodynamic effects of orally administered isosorbide dinitrate in patients with congestive heart failure. *Circulation,* **50,** 1020–1024.

Frohlich, E. D., and Scott, J. B. (1962). The local effect of glyceryl trinitrate, nitrite, papaverine and atropine upon coronary vascular resistance. *American Heart Journal,* **63,** 362–366.

Ganz, W., and Marcus, H. S. (1972). Failure of intracoronary nitroglycerin to alleviate pacing-induced angina. *Circulation,* **46,** 880–889.

Gold, H. K., Leinbach, R. C., and Sanders, C. A. (1972). Use of sublingual nitroglycerin in congestive heart failure following acute myocardial infarction. *Circulation,* **46,** 839–845.

Goodman, D. J., Rossen, R. M., Holloway, E. L., Alderman, E. L., and Harrison, D. C. (1974). Effect of nitroprusside on left ventricular dynamics in mitral regurgitation. *Circulation,* **50,** 1025–1032.

Gorlin, R., Brachfeld, N., Macleod, C., and Bopp, P. (1959). Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. *Circulation,* **19,** 705–718.

Gould, L., Reddy, C. V. R., Blatt, C. J., Gomprecht, R. F., and Hayt, D. B. (1975). Effects of phentolamine on coronary blood flow in patients with recent myocardial infarction. *British Heart Journal,* **37,** 647–651.

Gould, L., Reddy, C. V. R., Kalanithi, P., Espina, L., and Gomprecht, R. F. (1974). Use of phentolamine in acute myocardial infarction. *American Heart Journal,* **88,** 144–148.

Gould, L., Zahir, M., and Ettinger, S. (1969). Phentolamine and cardiovascular performance. *British Heart Journal,* **31,** 154–162.

Gray, R., Chatterjee, K., Vyden, J. K., Ganz, W., Forrester, J. S., and Swan, H. J. C. (1975). Hemodynamic and metabolic effects of isosorbide dinitrate in chronic congestive heart failure. *American Heart Journal,* **90,** 346–352.

Guiha, N. H., Cohn, J. N., Mikulic, E., Franciosa, J., and

Limas, C. J. (1974). Treatment of refractory heart failure with infusion of nitroprusside. *New England Journal of Medicine,* **291,** 587–592.

Harshaw, C. W., Grossman, W., Munro, A. B., and McLaurin, L. P. (1975). Reduced systemic vascular resistance as therapy for severe mitral regurgitation of valvular origin. *Annals of Internal Medicine,* **83,** 312–316.

Kelly, D. T., Delgado, C. E., Taylor, D. R., Pitt, V., and Ross, R. S. (1973). Use of phentolamine in acute myocardial infarction associated with hypertension and left ventricular failure. *Circulation,* **47,** 729–735.

Kerber, R. E., and Abboud, F. M. (1975). Effect of alterations of arterial blood pressure and heart rate on segmental dyskinesis during acute myocardial ischemia and following coronary reperfusion. *Circulation Research,* **36,** 145–155.

Kerber, R. E., Marcus, M. L., Ehrardt, J., and Abboud, F. M. (1976). Effect of intra aortic balloon counterpulsation on the motion and perfusion of acutely ischemic myocardium. An experimental echocardiographic study. *Circulation,* **53,** 853–859.

Killip, T., and Kimball, J. T. (1967). Treatment of myocardial infarction in a coronary care unit. *American Journal of Cardiology,* **20,** 457–464.

Lang, T. W., Meerbaum, S., Corday, E., Hashimoto, K., Davidson, R., Osher, J., and Katz, J. (1976). Comparative regional effects of intravenous and sublingual administration of nitroglycerin during acute myocardial ischemia. *American Journal of Cardiology,* **37,** 150.

Luebs, E. D., Cohen, A., Zaleski, E. J., and Bing, R. J. (1966). Effect of nitroglycerin, intensain, isoptin and papaverine on coronary blood flow in man. Measured by the coincidence counting technic and rubidium. *American Journal of Cardiology,* **17,** 535–541.

Majid, P. A., Sharma, B., and Taylor, S. H. (1971). Phentolamine for vasodilator treatment of severe heart-failure. *Lancet,* **2,** 719–724.

Mantle, J. A., Russell, R. O., Jr., Moraski, R. E., and Rackley, C. E. (1976). Isosorbide dinitrate for the relief of severe heart failure after myocardial infarction. *American Journal of Cardiology,* **37,** 263–268.

Mikulic, E., Franciosa, J. A., and Cohn, J. N. (1975). Comparative haemodynamic effects of chewable isosobide dinitrate and nitroglycerin in patients with congestive heart failure. *Circulation,* **52,** 477–482.

Miller, R. R., Vismara, L. A., Zelis, R., Amsterdam, E. A., and Mason, D. T. (1975). Clinical use of sodium nitroprusside in chronic ischemic heart disease. *Circulation,* **51,** 328.

Milnor, W. R. (1975). Arterial impedance as ventricular afterload. *Circulation Research,* **36,** 565–570.

Mueller, H., Religa, A., Evans, R., and Ayres, S. (1974). Metabolic changes in ischemic myocardium by nitroprusside. *American Journal of Cardiology,* **33,** 158.

Pepine, C. J., Nichols, W. W., Curry, R. C., and Conti, C. R. (1976). Reversal of premature mitral valve closure by nitroprusside infusion in severe aortic insufficiency: beat to beat pressure-flow and echocardiographic relationships. *American Journal of Cardiology,* **37,** 161.

Perret, Cl., Gardaz, J. P., Reynaert, M., Gimbert, F., and Enrico, J. F. (1975). Phentolamine for vasodilator therapy in left ventricular failure complicating acute myocardial infarction. Haemodynamic study. *British Heart Journal,* **37,** 640–646.

Ramanathan, B. K., Raina, S., Bodenheimer, M. M., Banka, V. S., and Helfant, R. H. (1975). The contrasting effects of nitroprusside and phentolamine on local contraction and degree of ischemia after coronary occlusion. *Clinical Research,* **23,** 569.

Ratshin, R. A., Rackley, C. E., and Russell, R. O., Jr. (1972). Hemodynamic evaluation of left ventricular function in shock complicating myocardial infarction. *Circulation,* **45,** 127–139.

Rowe, G. G., and Henderson, R. H. (1974). Systemic and coronary hemodynamic effects of sodium nitroprusside. *American Heart Journal,* **87,** 83–87.

Scheidt, S., Wilner, G., Fillmore, S., Shapiro, M., and Killip, T. (1973). Objective haemodynamic assessment after acute myocardial infarction. *British Heart Journal,* **35,** 908–916.

Shell, W. E., and Sobel, B. E. (1974). Protection of jeopardized ischemic myocardium by reduction of ventricular afterload. *New England Journal of Medicine,* **291,** 481–486.

Singh, J. B., Hood, W. B., and Abelmann, W. H. (1970). Beta-adrenergic-mediated inotropic and chronotropic actions of phentolamine. *American Journal of Cardiology,* **26,** 660.

Sniderman, A. D., Marpole, D. G. F., Palmer, W. H., and Fallen, E. L. (1974). Response of the left ventricle to nitroglycerin in patients with and without mitral regurgitation. *British Heart Journal,* **36,** 357–361.

Sonnenblick, E. H. (1962). Force-velocity relations in mammalian heart muscle. *American Journal of Physiology,* **202,** 931–939.

Swan, H. J. C., Forrester, J. S., Danzig, R., and Allen, H. N. (1970). Power failure in acute myocardial infarction. *Progress in Cardiovascular Disease,* **12,** 568–600.

Taylor, W. R., Forrester, J. S., Magnusson, P., Takano, T., Chatterjee, K., and Swan, H. J. C. (1975). The hemodynamic effects of nitroglycerin ointment in congestive heart failure. *Circulation,* **51** and **52,** Suppl. II, 36.

Walinsky, P., Chatterjee, K., Forrester, J., Parmley, W. W., and Swan, H. J. C. (1974). Enhanced left ventricular performance with phentolamine in acute myocardial infarction. *American Journal of Cardiology,* **33,** 37–41.

Weber, K. T., Ratshin, R. A., Janicki, J. S., Rackley, C. E., and Russell, R. O. (1973). Left ventricular dysfunction following acute myocardial infarction. A clinicopathologic and haemodynamic profile of shock and failure. *American Journal of Medicine,* **54,** 697–705.

Williams, D. O., Amsterdam, E. A., and Mason, D. T. (1975a). Hemodynamic effects of nitroglycerin in acute myocardial infarction. Decrease in ventricular preload at the expense of cardiac output. *Circulation,* **51,** 421–427.

Williams, D. O., Hilliard, G. K., Cantor, S. A., Miller, R. R., and Mason, D. T. (1975b). Comparison of nitroprusside and phentolamine in left ventricular impedance reduction therapy of cardiac failure. *Clinical Research,* **23,** 88.

Wolk, M. J., Scheidt, S., and Killip, T. (1972). Heart failure complicating acute myocardial infarction. *Circulation,* **45,** 1125–1138.

Zahir, M., and Gould, L. (1971). Phentolamine and beta adrenergic receptors. *Journal of Clinical Pharmacology,* **11,** 197–203.

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Haemodynamic effects of salbutamol and nitroprusside after cardiac surgery

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The haemodynamic effects of a continuous intravenous infusion of salbutamol (15 to 30 μg/min) and nitroprusside (50 to 100 μg/min) were compared in 9 patients after cardiac surgical operations. The mean falls in left atrial pressure and systemic vascular resistance were similar with the two drugs but salbutamol caused a greater increase in heart rate, maximum acceleration of aortic blood flow, and maximum rate of change of left ventricular power. Because these differences would cause greater myocardial oxygen consumption with salbutamol and because the infusion of salbutamol is less easily controlled, nitroprusside is the preferred drug after cardiac operations.

Drugs that cause vasodilatation and consequently a reduction in systemic vascular impedance (left ventricular afterload) have recently been advocated in a variety of circumstances in which cardiac function is abnormal. Advantageous effects have been reported in patients with acute myocardial infarction (Chatterjee *et al.*, 1973), chronic ischaemic heart disease (Miller *et al.*, 1975), refractory heart failure (Guiha *et al.*, 1974), mitral regurgitation and stenosis (Goodman *et al.*, 1974; Bolen *et al.*, 1975), and cardiomyopathy (Rossen *et al.*, 1976). Benefit from impedance reduction has also been claimed in patients who have undergone cardiac surgical operations, particularly in those with high systemic vascular impedance, raised left atrial pressure, or suspected subendocardial ischaemia. In such circumstances, Stinson *et al.* (1975) compared several vasodilators: intravenous nitroprusside produced a more favourable haemodynamic response than chlorpromazine, nitroglycerin, or trimetaphan.

Salbutamol is a relatively specific β_2-adrenergic receptor agonist and causes peripheral vasodilatation. The haemodynamic effects of a single intravenous dose have been reported in normal persons (Warrell *et al.*, 1970; Leitch *et al.*, 1976) and in patients with respiratory disease (Warrell *et al.*, 1970; Leitch *et al.*, 1976), myocardial infarction (Lal *et al.*, 1972), or mitral regurgitation (Gibson and Coltart, 1970). Salbutamol has also been advocated for use after cardiac operations. Yacoub and Boyland (1973) reported the effects of a single intravenous dose and Wyse *et al.* (1974) compared the effects of continuous intravenous infusions of salbutamol and isoprenaline but gave no details of the basal haemodynamic state of their patients before administration of the drug.

The present study was undertaken to measure the haemodynamic changes during a continuous intravenous infusion of salbutamol in patients soon after cardiac operations. A comparison was made with the effects of an infusion of nitroprusside because this drug has previously been recommended in similar circumstances (Stinson *et al.*, 1975).

Methods

Nine patients (7 male, 2 female; age range 36 to 64 years, mean 51 years) were studied. Five had aortocoronary bypass grafts inserted and 2 had had aortic and 2 mitral valve replacement. The patients were unselected consecutive surgical candidates in whom preoperative catheterisation had excluded left ventricular dyskinesia or valve disease other than that for which the operation was being performed. The exact nature of the investigation was explained to the patients in order to obtain informed consent.

The study began 24 to 36 hours after operation, at a time when the patients could be maintained for several hours in quiet undisturbed circumstances. During this period no additional drugs were given. One patient was receiving an inotropic agent (iso-

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prenaline 1 μg/min) and this was continued at constant rate throughout the study. Nitroprusside or salbutamol was diluted in 5 per cent dextrose and administered by infusion pump (Sage Instruments, Model 242) through a cannula in the internal jugular vein. Nitroprusside was prepared in the pharmacy of St. Thomas's Hospital.

After a control period of 20 minutes, during which the haemodynamic variables listed in Table 1 were required to be constant, nitroprusside was given. The infusion rate was adjusted to bring about a fall of mean left atrial pressure and a reduction of systemic vascular resistance of approximately 30 per cent. Systolic blood pressure was not permitted to fall below 80 mmHg or mean left atrial pressure below zero. The infusion was terminated if the heart rate rose above 135 beats/min. The dose varied between 50 and 100 μg/min. The infusion was maintained at constant rate for 15 minutes; after discontinuing the infusion, measurements were continued for a further 20 minutes. The values for the haemodynamic variables at the end of the infusion were compared with the means of those at the end of the initial control periods and those after 20 minutes off nitroprusside.

When the patient had again remained haemodynamically stable for 20 minutes, salbutamol was infused in a dose of 15 μg/min (8 patients) or 30 μg/min (1 patient) and continued for 45 minutes. Measurements at the end of this period were compared with those in the control period. Nitroprusside was always administered before salbutamol because it has a short clinical half-life (approximately one minute) whereas the effects of salbutamol last for several hours.

Aortic blood flow was measured with a precalibrated extractable electromagnetic blood flow probe (Carolina Medical Electronics, 900 Series). It was placed firmly around the aorta, 1 to 2 cm above the sinotubular junction, at the time of operation and maintained in position by a nylon snare. The end was brought out through the chest wall. Release of the snare and gentle traction enabled the probe to be removed (Williams *et al.*, 1972). The probe was connected to a flow meter (Carolina Medical Electronics, Model 601D).

Left atrial pressure was measured with a transducer (Statham 23P) connected to a fluid-filled line inserted in the left atrium at the time of operation. The reference level for pressure measurements was the sternal angle. Arterial pressure was measured with a Millar PC 350 catheter-tip micromanometer connected to a cannula in the radial or femoral artery. Arterial pressure and aortic flow signals, with simultaneous electrocardiogram, were processed 'on-line' by a small analogue computer (Bourne and Williams, 1975), recorded on tape (Philips, Analog 7 FM) and displayed on an oscilloscope. Heart rate, arterial and left atrial pressures, stroke volume, stroke work, and systemic vascular resistance were monitored continuously. Maximum rate of change of power and maximum acceleration of flow from the left ventricle during ejection were calculated by integration and differentiation of the pressure and flow signals (Stein and Sabbah, 1976). Any delay between the pressure and flow signals was eliminated by superimposition of the initial rise of both variables.

Results are expressed as mean ± SEM and were compared using Student's paired t test.

Results

The haemodynamic consequences of an infusion of nitroprusside and of salbutamol are illustrated in the Figure. Nitroprusside has a rapid onset of action which quickly subsides after withdrawal of the drug. By contrast the effects of salbutamol appear more slowly and persist for many minutes after the infusion has ceased. The pooled results are shown in Tables 1 and 2.

Salbutamol (Table 1) increased the cardiac index, but this was entirely attributable to a rise in heart rate and not to a change of stroke volume. Heart rate rose by a mean of 17 beats/minute. In 2 patients, neither of whom was the shortest or lightest in the group, the infusion of 15 μg/min was discontinued after 25 minutes when the heart rate rose above 135 beats/min. Systemic vascular resistance fell by 21 per cent and left atrial pressure by 40 per cent. Maximum acceleration of flow and maximum rate of change of power were both augmented.

Nitroprusside (Table 2) caused similar changes. The control values before the infusion of either drug were the same (Tables 1 and 2). Both drugs reduced the systemic vascular resistance and left atrial pressure, and neither increased the stroke index. However, there were important differences. The increase in heart rate with salbutamol (17 beats/min) was greater than with nitroprusside (6 beats/min) ($P < 0{\cdot}01$). Maximum acceleration of flow rose with salbutamol but not with nitroprusside ($P < 0{\cdot}05$). Salbutamol increased the maximum rate of change of power whereas nitroprusside had the reverse effect ($P < 0{\cdot}01$).

Discussion

After heart operations the management of patients with cardiovascular disturbances such as low cardiac output, peripheral constriction, raised left

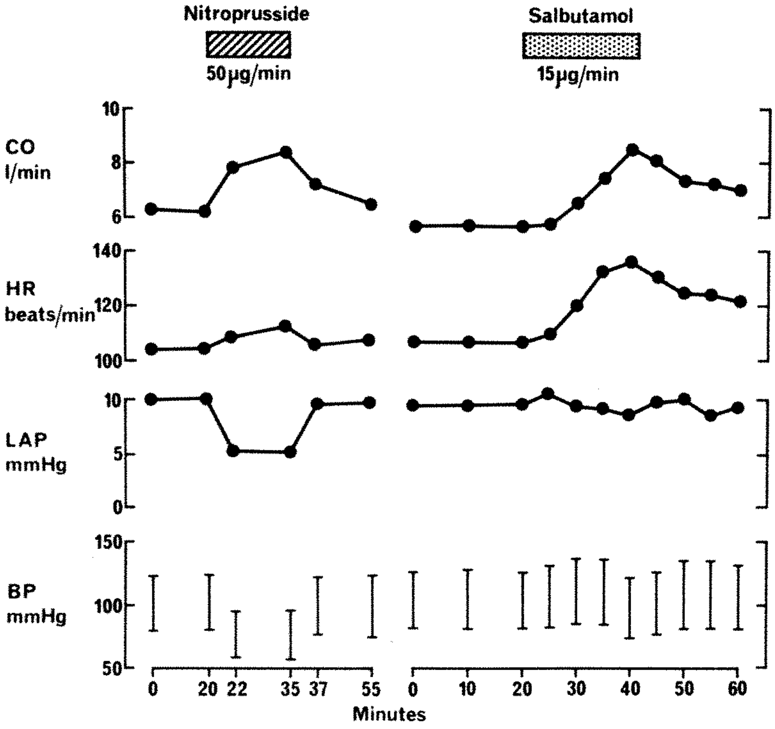

Fig. *The effects of a continuous intravenous infusion of nitroprusside and salbutamol are shown in the same patient. Nitroprusside caused a rapid fall of left atrial pressure (LAP) which was precisely reversible. Cardiac output (CO) increased and the blood pressure (BP) fell. A small increase of heart rate (HR) occurred. Salbutamol caused only a small fall of LAP and BP. In this patient the heart rate increased so much that the infusion was discontinued after 20 minutes.*

Table 1 *Haemodynamic variables before and during salbutamol administration*

	Control	*Salbutamol (15–30 µg/min)*	*Significance (P)*
Cardiac output (l/min per kg BW)	0·060 ±0·008	0·077 ±0·012	<0·05
Heart rate (beats/min)	94 ±4	111 ±6	<0·005
Stroke volume (ml)	50 ±8	51 ±8	NS
Systolic blood pressure (mmHg)	129 ±6	128 ±8	NS
Diastolic blood pressure (mmHg)	76 ±3	72 ±4	<0·02
Systemic vascular resistance (units*)	23 ±4	19 ±4	<0·005
Left atrial pressure (mmHg)	10 ±2	6 ±1	<0·05
Maximum acceleration (l s^{-2})	8·2 ±1·7	9·8 ±1·8	<0·001
Maximum rate of change of power (W/s)	110 ±25	141 ±34	<0·02

*Systemic vascular resistance (in arbitrary units) expressed as mean systemic arterial pressure (mmHg)/cardiac output (l/min).
BW = body weight.

Table 2 *Haemodynamic variables before and during nitroprusside administration*

	Control	*Nitroprusside (50–100 µg/min)*	*Significance (P)*
Cardiac output (l/min per kg BW)	0·064 ±0·010	0·071 ±0·010	<0·05
Heart rate (beats/min)	98 ±4	104 ±5	<0·005
Stroke volume (ml)	50 ±7	52 ±8	NS
Systolic blood pressure (mmHg)	132 ±6	111 ±8	<0·005
Diastolic blood pressure (mmHg)	76 ±3	67 ±3	<0·005
Systemic vascular resistance (units)	23 ±3	16 ±1	<0·005
Left atrial pressure (mmHg)	9 ±2	5 ±1	<0·01
Maximum acceleration (l s^{-2})	8·5 ±1	8·9 ±1	NS
Maximum rate of change of power (W/s)	135 ±30	100 ±20	<0·02

atrial pressure, or subendocardial ischaemia, is complex. Inotropic drugs such as isoprenaline are much used for some of these complications but their use has been criticised because the oxygen consumption of the myocardium is increased and pre-existing ischaemia may be increased (Maroko *et al.*, 1971). The reduction of systemic vascular impedance or left ventricular afterload by drugs which act as vasodilators is an alternative form of treatment. This has been shown to be beneficial in myocardial infarction (Chatterjee *et al.*, 1973), chronic heart failure (Guiha *et al.*, 1974; Miller *et al.*, 1975), and mitral valve disease (Goodman *et al.*, 1974; Bolen *et al.*, 1975). Such results, however, should not immediately be applied to other clinical situations since the overall haemodynamic response to such treatment is dependent on the pre-existing conditions, the pharmacological properties of the particular drug, the dose of the drug, the site of action, and reflex changes. Vasodilators may be advantageous to the myocardium for several reasons: reduction of systemic vascular impedance permits greater muscle shortening and reduces systolic left ventricular wall tension and left ventricular end-diastolic volume; a fall of left atrial pressure resulting from a venodilator effect reduces left ventricular end-diastolic volume, and in addition encourages greater blood flow in the subendocardial tissue during diastole, and may thus relieve pre-existing ischaemia in the subendocardial myocardium; a direct action of vasodilators on the coronary vasculature has been reported and blood flow to ischaemic segments of muscle may increase (Goldstein *et al.*, 1974). These many effects tend to result in a favourable change in the balance of oxygen supply and demand, but because of the complexity of the interactions among these and other factors, new drugs should be evaluated in each clinical situation in which they might be used. Nitroprusside has been advocated for use after cardiac operations (Stinson *et al.*, 1975), and our study was designed to compare nitroprusside and salbutamol in this clinical situation.

Salbutamol and nitroprusside both acted as vasodilators (Tables 1 and 2) and in the doses chosen the changes in systemic vascular resistance and in left atrial pressure were similar. However, salbutamol caused a substantially greater increase in heart rate, and stroke volume was unaltered by either drug. This effect might sometimes be beneficial but in general is detrimental since heart rate is an important determinant of oxygen consumption (Braunwald, 1971). This increase in heart rate with salbutamol occurs also in normal persons and in patients with respiratory failure (Warrell *et al.*, 1970; Leitch *et al.*, 1976). Oxygen consumption of the myocardium is increased further by salbutamol because of the increase in maximum acceleration of flow (20%) and maximum rate of change of power (28%). Maximum acceleration was unaffected by nitroprusside and maximum rate of change of power diminished (25%). Since stroke volume was unaltered and preload and afterload equally affected by the two drugs, these differences might be explained if salbutamol increased contractility in association with the greater change of heart rate—the Bowditch effect (Bowditch, 1871). Whatever the explanation, an increase in the maximum rate of change of power and heart rate are both expected to increase myocardial oxygen consumption. For these reasons and because the long duration of action of salbutamol does not allow precise control of the infusion, nitroprusside is the preferred drug.

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References

Bolen, J. L., Lopes, M. G., Harrison, D. C., and Alderman, E. L. (1975). Analysis of left ventricular function in response to afterload changes in patients with mitral stenosis. *Circulation*, **52**, 894–900.

Bourne, P. R., and Williams, B. T. (1975). A cardiac monitor combining flow and pressure measurement. *Biomedical Engineering*, **10**, 453–455.

Bowditch, H. P. (1871). Über die Eigenthümlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen. *Bericht über die Verhandlungen der Sächsischen Akademie der Wissenschaften zu Leipzig (Math. Phys. Kl.)*, **23**, 652.

Braunwald, E. (1971). Control of myocardial oxygen consumption: physiologic and clinical considerations. *American Journal of Cardiology*, **27**, 416–432.

Chatterjee, K., Parmley, W. W., Ganz, W., Forrester, J., Walinsky, P., Crexells, C., and Swan, H. J. C. (1973). Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. *Circulation*, **48**, 1183–1193.

Gibson, D. G., and Coltart, D. J. (1970). Haemodynamic effects of intravenous solbutamol in patients with mitral valve disease: comparison with isoprenaline and atropine. *Postgraduate Medical Journal*, **47**, Suppl. (March), 40–44.

Goldstein, R. E., Stinson, E. B., Scherer, J. L., Seningen, R. P., Grehl, T. M., and Epstein, S. E. (1974). Intraoperative coronary collateral function in patients with coronary occlusive disease: nitroglycerin responsiveness and angiographic correlations. *Circulation*, **49**, 298–308.

Goodman, D. J., Rossen, R. M., Holloway, E. L., Alderman, E. L., and Harrison, D. C. (1974). Effect of nitroprusside on left ventricular dynamics in mitral regurgitation. *Circulation*, **50**, 1025–1032.

Guiha, N. H., Cohn, J. N., Mikulic, E., Franciosa, J. A., and Limas, C. J. (1974). Treatment of refractory heart failure with infusion of nitroprusside. *New England Journal of Medicine*, **291**, 587–592.

Lal, S., Savidge, R. S., Davies, D. M., Ali, M. M., and Soni, V. (1972). Intravenous salbutamol and cardiogenic shock. *Lancet,* **1,** 853–854.

Leitch, A. G., Clancy, L. J., Costello, J. F., and Flenley, D. C. (1976). Effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal men. *British Medical Journal,* **1,** 365–367.

Maroko, P. R., Kjekshus, J. K., Sobel, B. E., Watanabe, T., Covell, J. W., Ross, J., and Braunwald, E. (1971). Factors influencing infarct size following experimental coronary artery occlusions. *Circulation,* **43,** 67–82.

Miller, R. R., Vismara, L. A., Zelis, R., Amsterdam, E. A., and Mason, D. T. (1975). Clinical use of sodium nitroprusside in chronic ischemic heart disease: effects on peripheral vascular resistance and venous tone and on ventricular volume, pump and mechanical performance. *Circulation,* **51,** 328–336.

Rossen, R. M., Alderman, E. L., and Harrison, D. C. (1976). Circulatory response to vasodilator therapy in congestive cardiomyopathy. *British Heart Journal,* **38,** 695–700.

Stein, P. D., and Sabbah, H. N. (1976). Ventricular performance measured during ejection: studies in patients of the rate of change of ventricular power. *American Heart Journal,* **91,** 599–606.

Stinson, E. B., Holloway, E. L., Derby, G., Oyer, P. E., Hollingsworth, J., Griepp, R. B., and Harrison, D. C. (1975). Comparative hemodynamic responses to chlorpromazine, nitroprusside, nitroglycerin, and trimethaphan immediately after open-heart operations. *Circulation,* **51–52,** Suppl. I, I-26–33.

Warrell, D. A., Robertson, D. G., Newton Howes, J., Conolly, M. E., Paterson, J. W., Beilin, L. J., and Dollery, C. T. (1970). Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. *British Medical Journal,* **1,** 65–70.

Williams, B. T., Sancho-Fornos, S., Clarke, D. B., Abrams, L. D., Schenk, W. G., Jr., and Barefoot, C. A. (1972). The Williams-Barefoot extractable blood flow probe: design, transducer characteristics, and clinical application in cardiac surgery. *Journal of Thoracic and Cardiovascular Surgery,* **63,** 917–921.

Wyse, S. D., Gibson, D. G., and Branthwaite, M. A. (1974). Haemodynamic effects of salbutamol in patients needing circulatory support after open-heart surgery. *British Medical Journal,* **3,** 502–503.

Yacoub, M. H., and Boyland, E. (1973). Cardiovascular effects of intravenous salbutamol after open heart operations. *Lancet,* **1,** 1260–1261.

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Evaluation of intracardiac recordings in diagnosis of impulse formation and concealed conduction in atrioventricular nodal bypass tracts

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Invasive electrophysiological studies were performed in 2 symptomatic patients with recurrent arrhythmias in which impulse formation presumably occurred within atrioventricular nodal bypass tracts. Case 1 had ectopic beats arising within, or close to, the upper end of a left-sided atrioventricular nodal bypass tract of the type described by Brechenmacher. In addition, this conduction was 'concealed' during sinus rhythm and right atrial pacing because the relatively prolonged right-to-left atrial conduction time allowed right atrial impulses to reach the His bundle via the atrioventricular node before they could do so through the atrioventricular nodal bypass tract. Case 2 had ectopic beats arising in a right-sided atrioventricular nodal bypass tract which did not conduct in either forward or retrograde directions, its presence being detected only when initiating impulses. However, it could not be determined whether this tract was an 'abnormal' atrio-His connection or a 'normal' transitional (atrio-atrioventricular nodal) tract. Though intracardiac studies complement body surface recordings, they should be interpreted with knowledge of their inherent limitations.

Most studies dealing with automaticity of accessory pathways have referred to ectopic beats arising in Kent tracts as reported in recent reviews on this subject (Przybylski *et al.*, 1975; Castellanos *et al.*, 1976). It seems appropriate, therefore, to discuss two possible examples of impulse formation in atrioventricular nodal bypass tracts.

Subjects and methods

Specialised intracardiac studies were performed in two symptomatic patients referred for investigation. The procedure was explained and informed consent obtained. As outlined in previous communications from our department, one catheter electrode was used to pace, alternatively, the atria and ventricles (Castellanos *et al.*, 1971, 1973, 1977; Agha *et al.*, 1976). Additional catheters were introduced to record the electrical activity of the high right atrium (HRA), the left atrium (LA) via the proximal coronary sinus, the area of the His bundle (HBE), and the right ventricular apex (RVA).

The following intervals were measured *during sinus rhythm* (number in parentheses indicate normal values in our laboratory):

(a) HRA–septal low right atrium (LRA): from onset of HRA electrogram to beginning of atrial electrogram recorded by the HBE lead (20 to 45 ms) = conduction time from close to the sinus node to septal LRA in the vicinity of the atrioventricular node.

(b) LRA–LA interval: from onset of the LRA electrogram to the onset of the left atrial electrogram recorded by the catheter electrodes in the proximal coronary sinus (>20 ms). This interval does not represent linear conduction time from low right atrium to left atrium but differences in arrival of excitation at the recording sites.

(c) LRA–H interval: from the beginning of the atrial to the onset of the His bundle electrograms in the HBE lead (55–120 ms) = atrioventricular nodal conduction time.

(d) HV interval: from the beginning of the His bundle electrogram to the onset of ventricular depolarisation in whichever lead (surface or intracardiac) it occurred first (35–55 ms) = conduction time from His bundle to the earliest site of (left or right) ventricular activation.

(e) H–RVA interval: from beginning of the His bundle electrogram (H) to that of the electrogram recorded by the catheter in the right

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ventricular apex (RVA) (55–75 ms) = conduction time through His bundle, right bundle-branch and that part of the ordinary ventricular muscle located between the site of exit (from the right bundle-branch) and the recording electrodes (Castellanos *et al.*, 1973).

During RVA pacing at the right ventricular apex retrograde activation of the atria by the impulse traversing the atrioventricular node (from the His bundle) occurs in an LRA–LA–HRA sequence (Agha *et al.*, 1976; Amat-y-Leon *et al.*, 1976; Gallagher *et al.*, 1976). When the H–LRA intervals exceed 55 ms (thus excluding retrograde conduction via atrioventricular nodal bypass tract) the corresponding values are: LRA–LA: 20–50 ms; LRA–HRA: 35–75 ms (Agha *et al.*, 1976).

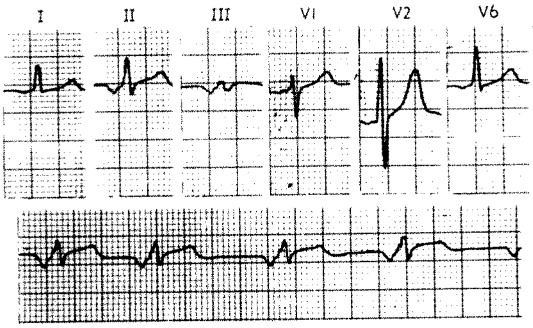

Fig. 1 *Case 1. Automatic ectopic rhythm with negative P waves in leads I, II, III, aVF (bottom strip), and V2–V6 showing short PR intervals and normal QRS complexes. The surface electrocardiographic pattern is that which has been attributed to coronary sinus, low left atrial, or atrioventricular junctional rhythms.*

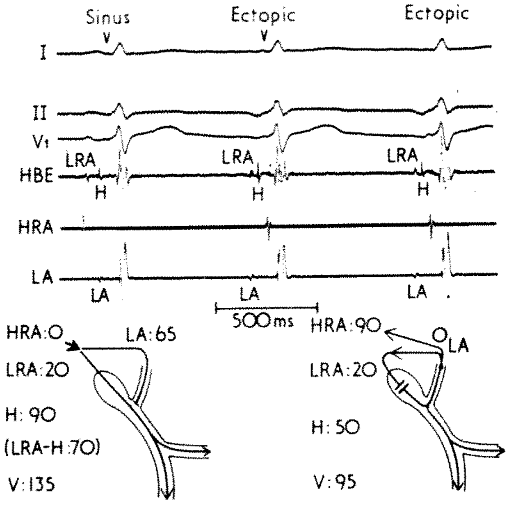

Fig. 2 *Case 1. Sinus beats conducted through the atrioventricular node (left) and ectopic beats presumably originating in the upper end of a left sided atrioventricular nodal bypass tract. HRA, high right atrium; HBE, His bundle electrographic lead; LA, left atrium; LRA, low (septal) right atrium; H, His bundle; V, onset of ventricular depolarisation. In this Fig. all intervals are expressed in ms from the moment of inscription of the first recorded atrial electrogram (0).*

It should also be noted that a decrease in St1–St2 intervals produces a progressive and proportional increase of the St2–LRA2, St2–LA2 and St2–HRA2 intervals with H2 (when and if recorded) appearing in front of LRA2 at similar (or longer; but definitely not shorter) intervals (Castillo and Castellanos, 1970).

Case descriptions

CASE 1

Electrocardiograms from this 23-year-old man with palpitations since childhood showed, almost persistently, an automatic rhythm characterised by negative P waves in leads I, II, III, and V2 to V6 (Fig. 1, top). The QRS complexes had normal morphology and duration (90 ms). The PR interval measured 95 ms while the ectopic rate varied from 75 to 95/min (lead aVF in Fig. 1, bottom).

An alternation between ectopic and sinus rhythms occurred during the performance of the intracardiac studies. Sinus beats (first in Fig. 2) showed upright P waves in lead II with a normal (HRA–LRA–LA) sequence of atrial activation. The duration of the conduction intervals and ventricular complexes was also normal, namely: PR = 135 ms; HRA–LRA = 20 ms; LRA = 70 ms; HRA–H = 90 ms; H–V = 45 ms and QRS = 95 ms.

In contrast, the third, ectopic, beat had a (retrograde) atrial activation pattern characterised by inscription of the left atrial electrogram 20 and 90 ms ahead of the LRA and HRA electrograms, respectively. If it is assumed that this impulse arose close to the atrial end of a left-sided atrioventricular nodal bypass tract (as shown in the right-sided diagram) then the LA–H interval of 50 ms can be used as a rough measure of forward conduction time through the atrioventricular nodal bypass tract. This value explains why sinus beats reached the His bundle through the atrioventricular node since (as shown in the left-sided diagram) the time needed by the HRA impulse to activate the His bundle via this structure (*90 ms:* HRA–LRA of 20 ms + LRA–H of 70 ms) was *less* than the time required to reach the His bundle via the atrioventricular nodal bypass tract (*115 ms:* HRA–LA of 65 ms + LA–H of 50 ms).

Therefore, in the ectopic beat, the short (30 ms)

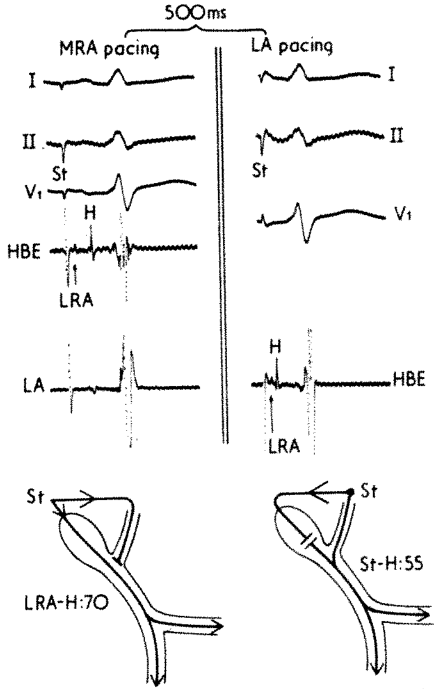

Fig. 3 *Case 1. Mid right atrial (MRA), and left atrial (LA) pacing at a basic cycle length of 600 ms showing conduction to the His bundle through the atrioventricular node bypass tract from the left atrium and through the atrioventricular node from MRA. All values in ms.*

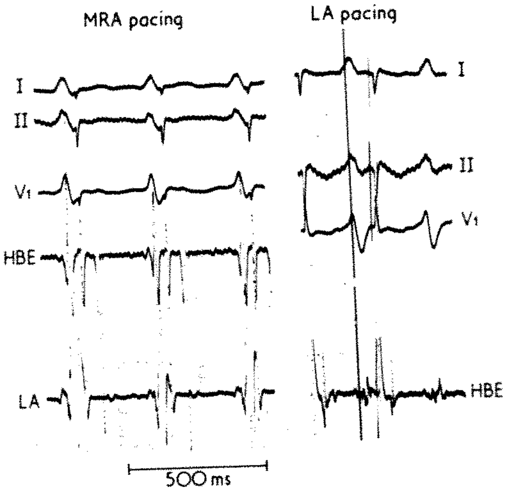

Fig. 4 *Mid right atrial (MRA) and left atrial (LA) pacing at the maximal rate capable of producing 1:1 atrioventricular conduction, namely, 175/min from MRA and 225/min from left atrium.*

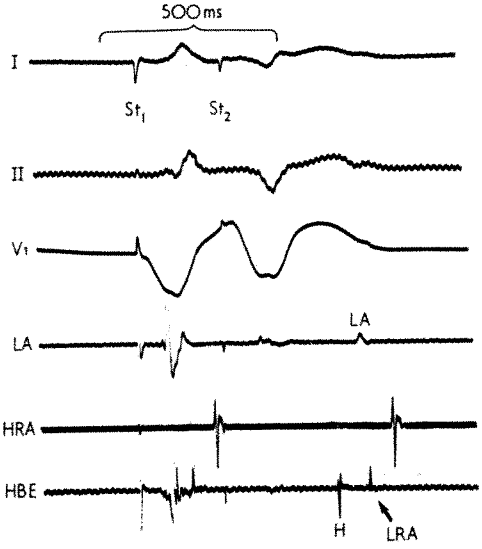

Fig. 5 *Case 1. Retrograde atrial activation pattern during ventricular pacing with the extrastimulus method. Note that the premature (St2) impulse activated the His bundle with considerable infra-His delay, thereafter reaching the left atrium (through the atrioventricular node bypass tract) ahead of the low right atrium. The retrograde atrial arrival of activation sequence was similar to that of ectopic beats in Fig. 2, right.*

interval elapsing between inscription of LRA and H did not represent linear conduction time from LRA to His bundle, but the difference in the time of arrival of excitation at the corresponding sites.

The different configuration of the atrial deflections in the HBE and HRA leads in the ectopic, as compared with sinus beats, supports these assumptions. Moreover, during left atrial pacing (Fig. 3, right) the St(LA)–H interval had more or less the same value (55 ms) as the LA–H interval of the ectopic beats shown in Fig. 2, right. On the other hand, mid right atrial stimulation (Fig. 3, left) resulted in LRA–H intervals (70 ms) similar to those of sinus beats. The corresponding HV intervals and QRS complexes were normal when either right or left atrium was paced (Fig. 3).

Pacing studies showed that 1:1 atrioventricular conduction occurred up to rates of 225 and 175/min from the left atrium and mid right atrium, respectively (Fig. 4).

During ventricular pacing with the extrastimulus technique the retrograde atrial activation sequence was similar to that of the ectopic beats in Fig. 2 since the LA2–LRA2 and LA2–HRA2 intervals measured

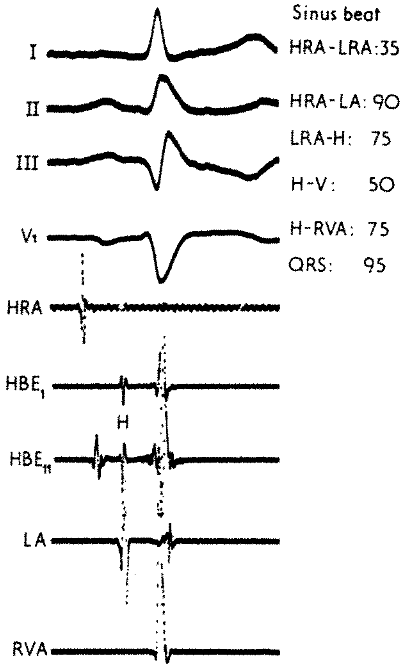

Fig. 6 *Case 2. Sinus rhythm with normal conduction intervals and control QRS complex.*

20 and 90 ms, respectively (Fig. 5). This sequence was maintained as the St1–St2 intervals were decreased in spite of the fact that the St2–LA2, St2–LRA2, and St2–HRA2 showed a concomitant (and proportional) increase presumably because of infra-His bundle delay since, when (at the shorter St1–St2 intervals) retrograde activation of the His bundle occurred, the St2–H2 increased but the H2–LA2 kept a fixed value of 50 ms (Fig. 5).

To summarise, the findings in this case are compatible with a left-sided atrioventricular nodal bypass tract (Brechenmacher, 1976) conducting in a forward direction (preferentially from the left atrium) as well as in a retrograde direction. Spontaneous impulse formation producing the ectopic beats could have occurred at, or close to, the atrial end of the atrioventricular nodal bypass tract.

CASE 2

This 56-year-old man with old inferior wall myocardial infarction and dizzy spells had ectopic beats and short runs of supraventricular tachycardia. During sinus rhythm the atria were activated in the normal fashion (Fig. 6). Right atrial pacing was possible with 1:1 atrioventricular response and progressive increments of AH until a rate of 155/min was reached at which moment the atria failed to respond. Thus, the exact rate at which atrioventricular Wenckebach occurred could not be determined.

As in case 1, values for the retrograde activation intervals were determined (during ventricular pacing with the extrastimulus technique) from the wavefronts elicited by St2 since the corresponding electrograms were best seen in premature beats delivered at short coupling intervals (Fig. 7, left). That the impulse reaching the His bundle (from the ventricles) activated the atria retrogradely through the atrioventricular node was suggested by the normal H–LRA interval of 70 ms and by inscription of the LRA electrogram 40 and 70 ms, respectively, before that of LA and HRA. Moreover, the St2–LRA2, St2–LA2 and St2–HRA2 showed a concomitant increase (while the H2L–RA2 interval remained constant) as the St1–St2 intervals were decreased.

This patient also had His bundle beats (Fig. 7, right) during which the surface P wave was buried within the ventricular complexes. Because the HV and H–RVA intervals, as well as QRS morphology,

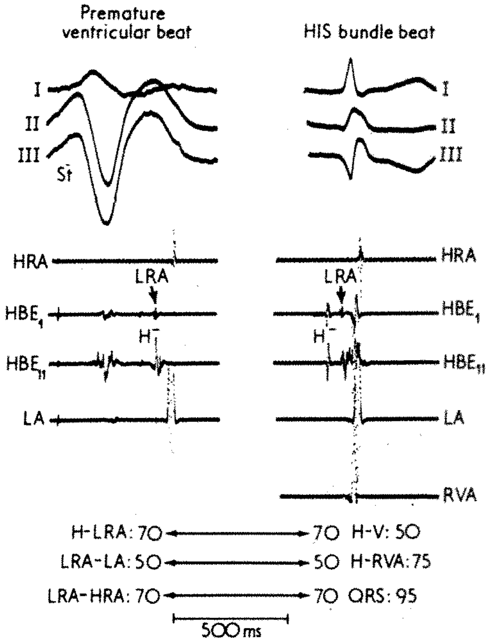

Fig. 7 *Case 2. Retrograde atrial activation pattern of impulses emerging from the atrioventricular node in a ventriculo-atrial direction. The left sided panel shows the QRS complexes produced by premature St2 impulses delivered to the right ventricular apex (RVA). The right sided panel depicts a spontaneous His bundle beat with HV and H–RVA intervals similar to those of sinus beats (Fig. 6).*

were similar to those of sinus beats (Fig. 6) it was inferred that the impulse originating in the His bundle reached the ventricles through the His-Purkinje system in a normal fashion. That the H–LRA, LRA–LA, and LRA–HRA intervals had the same duration as those recorded during retrograde (VA) conduction of premature ventricular beats (Fig. 7, left) indicates that the atria were also depolarised retrogradely by the impulse emerging from the atrioventricular node.

In addition, there were other ectopic beats in which the LRA electrogram preceded H by an interval of only 20 ms (Fig. 8). The P wave (appearing at a short interval in front of QRS) seemed to have been slightly negative in all three standard leads. The normal duration of the HV and H–RVA intervals as well as of the QRS complexes indicated that the impulse reaching the His bundle activated the ventricles through the His-Purkinje system as during sinus rhythm (Fig. 6).

These ectopic beats did not originate in the His bundle (or ventricles) because the LRA was activated *before* the His bundle (and also before the left atrium). Moreover, the different duration (in respect to those of the beats shown in Fig. 7) of the LRA–LA and LRA–HRA intervals (70 and 90 ms, respectively) indicates that the atria were not activated by the impulse emerging from the atrioventricular node.

To summarise, the events occurring in Fig. 7 suggest that these beats arose in a right-sided atrioventricular nodal bypass tract. From its origin the impulse spread toward right atrium and His bundle reaching the former slightly before the latter. Thus, the (short) LRA–H did not represent linear conduction time from one site to the other but differences in arrival of excitation at the corresponding sites.

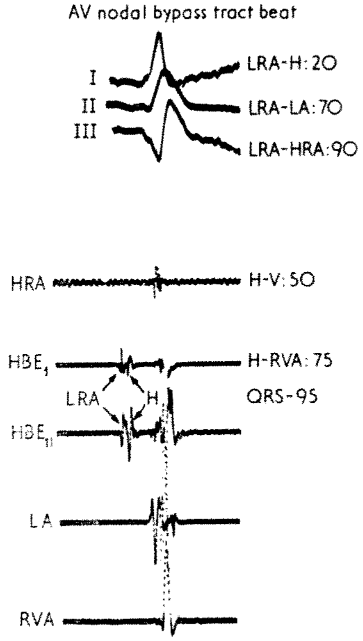

Fig. 8 *Case 2. Ectopic beat presumably arising in a right sided atrioventricular node bypass tract. The short LRA–H did not represent linear conduction time from one site to another but differences of arrival of excitation at the recording electrodes from the site of origin within the atrioventricular node bypass tract.*

Discussion

Case 1 probably had an abnormal left-sided atrio-His tract of the type described by Brechenmacher in 1976 showing preferential (exclusively forward) conduction from the left atrium: the atrioventricular nodal bypass tract conduction was 'concealed' during sinus rhythm and right atrial pacing. This phenomenon was the result of the relatively longer right atrium to left atrium conduction time (as compared with the right atrium to low right atrium conduction time) which allowed the right atrial impulses to reach the His bundle through the atrioventricular node before they had time to do so through the atrioventricular nodal bypass tract (Fig. 2).

Brechenmacher (1976) reported on the electrophysiological and pathological findings in 2 patients with atrioventricular nodal bypass tract which differed from the so-called James fibres in three aspects: (1) the atrio-His tracts were located on the left side of the His bundle whereas the James fibres were located on the right side of the septum; (2) atrio-His tracts penetrated the His bundle, whereas the fibres described by James penetrated the atrioventricular node and (3) the histological structure of these tracts was that of ordinary atrial myocardium, whereas James described tracts predominantly composed of Purkinje fibres.

In case 1 (Fig. 5) retrograde conduction occurred only through the left-sided atrioventricular nodal bypass tract and not via the atrioventricular node or a left-sided Kent tract (Gallagher *et al.*, 1975; Agha *et al.*, 1976; Amat-y-Leon *et al.*, 1976). The former was excluded because the low right atrium was not inscribed ahead of the left atrium.

During ventriculo-atrial conduction through a left-sided Kent tract, the left atrium also occurs before the low right atrium. However, in these cases the St2–LA2 and St2–LRA2 intervals do not show a progressive and significant increase with shortening of the St1–St2 intervals, and H2, when seen, is not inscribed at a fixed interval ahead of LA2 and

LRA2. In fact, it might even appear after LRA2 (Castillo and Castellanos, 1970).

In case 2, the right-sided atrioventricular nodal bypass tract was 'concealed' in the sense that it did not conduct in either forward or retrograde directions. The presence of this atrioventricular nodal bypass tract was detected only because it initiated impulses, as shown by the retrograde atrial activation pattern (Fig. 8) which was different from that of impulses emerging from the atrioventricular node (Fig. 7). However, it could not be determined whether the ectopic beats arose in an *abnormal* atrio-His bundle tract or in one of the multiple transitional fibres which *normally* bypass part of the compact atrioventricular node (Anderson *et al.*, 1975).

It should be stated that inscription of low right atrium ahead of left atrium by itself is not diagnostic of retrograde atrioventricular nodal conduction. This sequence can also occur when a right-sided Kent bundle is present (Gallagher *et al.*, 1975). In these cases the St2–LRA2 and St2–LA2 intervals do not show a progressive increase as the St1–St2 interval is shortened and H2, when seen, is not inscribed at a fixed interval ahead of LRA2.

The ectopic beats in Fig. 1, 2, and 8 had a surface electrocardiographic pattern characterised by a short PR interval with negative P waves in all three standard leads and normal QRS complexes. The genesis of this pattern has been a subject of considerable debate and speculation since it has been attributed to many different mechanisms, namely: atrioventricular nodal rhythm, coronary sinus rhythm, low atrial rhythm, etc. The most extensive review on this subject was made by Scherf and Schott (1973) (specifically see pages 116, 117, and 129 to 131).

We agree with these authors, as well as with Watson (quoted by Scherf and Schott, 1973, page 551) who stated that, 'in patients with spontaneously occurring arrhythmias it is not possible to differentiate left atrial, from A–V junction, or coronary sinus, rhythms with any degree of certainty, by means of scalar electrocardiography and perhaps vectorcardiography.'

Intracardiac electrograms add another dimension to body surface recordings. The findings in cases 1 and 2 suggest that the pattern of 'atrioventricular junctional rhythm with preceding activation of the atria can also result from impulse formation within an atrioventricular nodal bypass tract. This assumption cannot be proven conclusively but is supported by the reports of Sherf and James (1966, 1969) who first suggested that ectopic beats could arise in the tracts that *normally* bypass part of the atrioventricular node.

Although specialised intracardiac studies did show that conduction through an atrioventricular nodal bypass tract could be 'concealed', they also have limitations. Foremost among these is that the exact site of impulse formation cannot be determined (using catheter electrodes) with the same degree of precision as if one were to be using roving endocardial electrodes for mapping purposes with the atria exposed during cardiopulmonary bypass (Kupersmith *et al.*, 1974). Thus, in case 1 a coronary sinus, or low left atrial, origin with preferential conduction to His bundle via a closely located left-sided atrioventricular nodal bypass tract (though less likely) could not be totally excluded.

Moreover, the degree of penetration into the coronary sinus required to record left atrial potentials cannot be determined exactly. Right atrial potentials are recorded immediately before entrance to the coronary sinus, as well as from its 'os' and within a nondetermined distance within the coronary sinus itself. Because the interatrial septum lies at an angle of approximately 45° to the frontal plane and the left atrium lies as much behind it as it does the right atrium (Walmsley and Watson, 1966a, b) one cannot use, exclusively, the spatial (right or left) relation between the catheter electrode intended to be placed into the coronary sinus and the catheter located over the septal surface of the right atrium to determine when the former starts to record left atrial potentials.

Recording several bipolar electrograms from the distal and proximal coronary sinus as stressed by Gallagher *et al.* (1975, 1976) is more selective in this respect. In previous reports from our department we considered that catheter electrodes were positioned behind the left atrium if pacing through them produced negative P waves in all three standard leads (Agha *et al.*, 1972, 1976).

The limitations of the catheter techniques, just described, do not invalidate the assumption made in this study. On the contrary, they should be recognised as useful guidelines for future studies oriented toward the analysis of the mechanism of spontaneous ectopic impulse formation in normal atrioventricular junctional tissues or in abnormal atrio-His tracts.

We are indebted to Dr. Claude Brechenmacher for bringing to our attention before publication, his findings on the first two patients in whom the presence of *left*-sided atrio-His tracts was first detected by electrophysiological and anatomical studies.

References

Agha, A. S., Befeler, B., Castellanos, A. M., Sung, R. J., Castillo, C. A., Myerburg, R. J., and Castellanos, A. (1976). Bipolar catheter electrograms for study of retrograde atrial activation pattern in patients without pre-excitation syndromes. *British Heart Journal,* **38,** 641–645.

Agha, A. S., Castillo, C. A., Castellanos, A., Jr., Myerburg, R. J., and Tessler, M. P. (1972). Supernormal conduction in the human atria. *Circulation,* **46,** 522–527.

Amat-y-Leon, F., Dhingra, R. C., Wu, D., Denes, P., Wyndham, C., and Rosen, K. M. (1976). Catheter mapping of retrograde atrial activation. Observations during ventricular pacing and A–V nodal re-entrant paroxysmal tachycardia. *British Heart Journal,* **38,** 355–362.

Anderson, R. H., Becker, A. E., Brechenmacher, C., Davies, M. J., and Rossi, L. (1975). The human atrioventricular junctional area. A morphological study of the A–V node and bundle. *European Journal of Cardiology,* **3,** 11–25.

Brechenmacher, C. (1976). Correlation between electrophysiology and anatomy in Wolff-Parkinson-White syndrome. Presented at the European Congress of Cardiology, Amsterdam, June 1976.

Castellanos, A., Jr., Agha, A. S., Befeler, B., Castillo, C. A., and Berkovits, B. V. (1973). A study of arrival of excitation at selected ventricular sites during human bundle branch block using close bipolar catheter electrodes. *Chest,* **63,** 208–213.

Castellanos, A., Jr., Castillo, C. A., Agha, A. S., and Tessler, M. P. (1971). His bundle electrograms in patients with short P–R intervals, narrow QRS complexes, and paroxysmal tachycardias. *Circulation,* **43,** 667–678.

Castellanos, A., Sung, R. J., Befeler, B., Mayorga-Cortes, A., Conde, C., Mallon, S. M., and Myerburg, R. J. (1977). Intermittent A–V conduction disturbances in patients with A-V nodal bypass tracts. Possible mechanisms of unusual variant of tachycardia-bradycardia syndrome. *British Heart Journal,* **39,** 38–43.

Castellanos, A., Sung, R. J., Castillo, C. A., Agha, A. S., Befeler, B., and Myerburg, R. J. (1976). His bundle recordings in diagnosis of impulse formation in Kent and Mahaim tracts. *British Heart Journal,* **38,** 1173–1178.

Castillo, C. A., and Castellanos, A., Jr. (1970). Retrograde activation of the His bundle during intermittent paired ventricular stimulation in the human heart. *Circulation,* **42,** 1079–1092.

Gallagher, J. J., Gilbert, M., Svenson, R. H., Sealy, W. C., Kasell, J., and Wallace, A. G. (1975). Wolff-Parkinson-White syndrome: the problem, evaluation and surgical correction. *Circulation,* **51,** 767–785.

Gallagher, J. J., Sealy, W. C., Wallace, A. G., and Kasell, J. (1976). Correlation between catheter electrophysiological studies and findings on mapping of ventricular excitation in Wolff-Parkinson-White Syndrome. In *The Conduction System of the Heart, Structure, Function and Clinical* Implications, pp. 588–612. Ed. by H. J. J. Wellens, K. I. Lie, and M. J. Janse. Stenfert Kroese, B. V. Leiden.

Kupersmith, J., Krongrad, E., Bowman, F. O., Jr., Malm, J., and Waldo, A. L. (1974). Pacing the human cardiac conduction system during open-heart surgery. *Circulation,* **50,** 499–506.

Przybylski, J., Chiale, P. A., Quinteiro, R. A., Elizari, M. V., and Rosenbaum, M. B. (1975). The occurrence of phase-4 block in the anomalous bundle of patients with Wolff-Parkinson-White syndrome. *European Journal of Cardiology,* **3,** 267–280.

Scherf, D., and Schott, A. (1973). *Extrasystoles and Allied Arrhythmias,* 2nd ed., pp. 116, 117, and 129–131. Wm. Heinemann, London.

Sherf, L., and James, T. N. (1966). A new look at some old questions in clinical electrocardiography. *Henry Ford Hospital Medical Bulletin,* **14,** 265–293.

Sherf, L., and James, T. N. (1969). A new electrocardiographic concept: synchronized sinoventricular conduction. *Diseases of the Chest,* **55,** 127–140.

Walmsley, R., and Watson, H. (1966a). The outflow tract of the left ventricle. *British Heart Journal,* **28,** 435–447.

Walmsley, R., and Watson, H. (1966b). The medial wall of the right atrium. *Circulation,* **34,** 400–411.

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Cardiomyopathic syndrome due to coronary artery disease[1]

I: Relation to angiographic extent of coronary disease and to remote myocardial infarction

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The relation between the extent of angiographic coronary artery disease and the presence of chronic heart failure in patients with coronary artery disease has not hitherto been clearly elucidated. In the present study clinical, ventriculographic, and coronary arteriographic features are compared in 84 patients with coronary artery disease. The extent of coronary disease is measured by the angiographic jeopardy score, which expresses how many of six coronary arterial segments are jeopardised by significant (>70% estimated luminal area reduction) proximal stenoses. Each jeopardised segment is counted as 2 points.

Thirty of the 84 patients had clinical evidence of chronic heart failure, all of whom were classified as having a cardiomyopathic syndrome caused by coronary artery disease since all had significant reduction of the left ventricular ejection fraction (<0·48) because of multiple and widespread left ventricular wall motion abnormalities. There were no patients in this study with chronic heart failure from other causes (e.g. isolated ventricular aneurysm).

The mean jeopardy score in the patients with cardiomyopathy was much higher than in the patients without cardiomyopathy ($10{\cdot}7 \pm 0{\cdot}4$ vs $5{\cdot}3 \pm 0{\cdot}6$, $P<0{\cdot}01$), and all patients with cardiomyopathy had a jeopardy score ≥ 8. Distal coronary artery disease was unrelated to the presence or absence of cardiomyopathy ($0{\cdot}5 \pm 0{\cdot}2$ vs $0{\cdot}4 \pm 0{\cdot}2$ diseased distal vessels per patient). Cardiomyopathy was strongly associated with the occurrence of multiple myocardial infarcts ($1{\cdot}9 \pm 0{\cdot}3$ myocardial infarcts per patient) in the group with cardiomyopathy and $0{\cdot}9 \pm 0{\cdot}2$ myocardial infarcts per patient in the group without it; 19 of 30 (64%) patients with cardiomyopathy had ≥ 2 myocardial infarcts, whereas 11 of 54 (20%) without had ≥ 2 myocardial infarcts ($P<0{\cdot}001$).

The findings of this study, that cardiomyopathy due to coronary artery disease is specifically related to the extent of proximal coronary artery disease and to the occurrence of multiple myocardial infarcts, constitute reasons for distinguishing this cardiomyopathic syndrome from the several other causes of chronic heart failure in coronary artery disease.

The angiographic scoring system used here, which more precisely relates the extent of coronary disease to the extent of left ventricle involved, was a stronger predictor of the presence or absence of the cardiomyopathic syndrome than the 1, 2, 3-vessel disease notation.

It is well known that patients with coronary artery disease may develop chronic heart failure. However, the relation between the extent of left ventricular dysfunction in such patients and the corresponding extent of coronary artery disease as shown by coronary angiography has not been clearly elucidated. Reported studies have come to differing conclusions. Proudfit and co-workers (1968) found that, if patients with extracardiac factors (severe anaemia, etc.) or isolated aneurysms were excluded, chronic heart failure in coronary artery disease was

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always associated with severe 2- or 3-vessel disease. Other investigators, however, have emphasised that there is little relation between clinical heart failure, or between the haemodynamic and ventriculographic correlates of heart failure, and the extent of coronary artery disease (Herman *et al.*, 1967; Baxley *et al.*, 1971; Cohn *et al.*, 1974b).

The present study compares clinical, ventriculographic, and arteriographic features in 84 patients with coronary artery disease. In particular, the purpose of this study is to analyse the extent of angiographic coronary disease in a subgroup of patients with coronary artery disease and chronic heart failure—those with multiple and widespread left ventricular wall motion abnormalities present in enough degree to reduce significantly the left ventricular ejection fraction at rest. We refer to this condition as 'cardiomyopathy due to coronary artery disease' in order to distinguish it from other causes of left heart failure in coronary artery disease and because it resembles idiopathic cardiomyopathy on ventriculography. We will also examine the relation of this cardiomyopathic syndrome to previous myocardial infarction.

Methods

PATIENT POPULATION

The study population consists of 84 patients shown by coronary angiography to have significant coronary artery disease affecting at least one major coronary artery. Since these patients were also selected for purposes of another study (Dash *et al.*, 1977), involving a comparison of coronary disease in patients with and without diabetes mellitus, one half had evidence of diabetes mellitus.

The clinical indications for angiographic study in these patients were representative of the clinical indications for angiography generally applicable in our institution. Seventy-four patients had angina of effort. Sixty-two patients had had one or more hospital admissions for unstable angina (prolonged chest pain without evidence of myocardial infarction, or a recent change in the frequency of angina). Nine patients were studied because of symptoms of heart failure and did not have disabling angina.

There were 72 men and 12 women. The mean age of the 84 patients was 54 years (range 33 years to 68 years). Twenty-one patients were known to have a history of persistent or labile hypertension (systolic blood pressure $\geq$150 mmHg, diastolic blood pressure $\geq$ 95mmHg, or both).

EVALUATION OF CLINICAL DATA

The medical record and electrocardiograms of each patient were carefully reviewed. Signs and symptoms of heart failure, as well as histories of digitalis and diuretic administration, were noted (see below).

Myocardial infarcts were defined as transmural or non-transmural. The former were diagnosed only in the presence of electrocardiographic Q waves of at least 0·04 s in duration; or, if Q waves were equivocal, akinesis or dyskinesis of the appropriate segment of the left ventriculogram and a typical history. Non-transmural infarcts were diagnosed when typical serum enzyme changes were unaccompanied by the evolution of Q waves.

Electrocardiographic left atrial enlargement was defined as terminal P wave negativity in lead V1 exceeding 0·03 mm/s.

RADIOLOGICAL ASSESSMENT

Coronary arteriograms, left ventriculograms, and plain chest films were viewed by one of us (R.E.D.) without knowledge of the clinical status of the patient.

All patients had chest *x*-ray films which were assessed for size of cardiac chambers and signs of pulmonary venous hypertension.

Selective coronary angiography was performed by either the Sones or Judkins techniques. Single-plane left ventriculograms were performed in the right anterior oblique projection. Three patients had biplane ventriculography. Three patients did not have ventriculograms (none of these patients had clinical manifestations suggesting left heart failure). Left ventricular volumes were measured by the modified area-length method of Sandler and Dodge (1968), using outlines of estimated end diastolic and end systolic cine frames.

The ejection fraction (left ventricular stroke volume divided by left ventricular end diastolic volume) was calculated for each ventriculogram. Large ventricles often were not all encompassed on a single cine frame. In these cases, ventricular outlines were drawn by using a composite of end systolic and end diastolic frames from several cardiac cycles. This method is probably less precise than when the ventricle can be outlined on single frames and for this reason absolute volumes are not reported. Five of the ventriculograms in which several cardiac cycles were used to complete end diastolic and end systolic outlines were selected at random and shown in blinded fashion to the same observer (R.E.D.) more than 18 months after his initial assessment. The difference in calculated ejection fraction between these two sets of observations averaged 0·03 (range 0·01 to 0·06). The same ventriculograms were also shown in blinded fashion to an independent observer. The difference between ejection fractions calculated from this set of

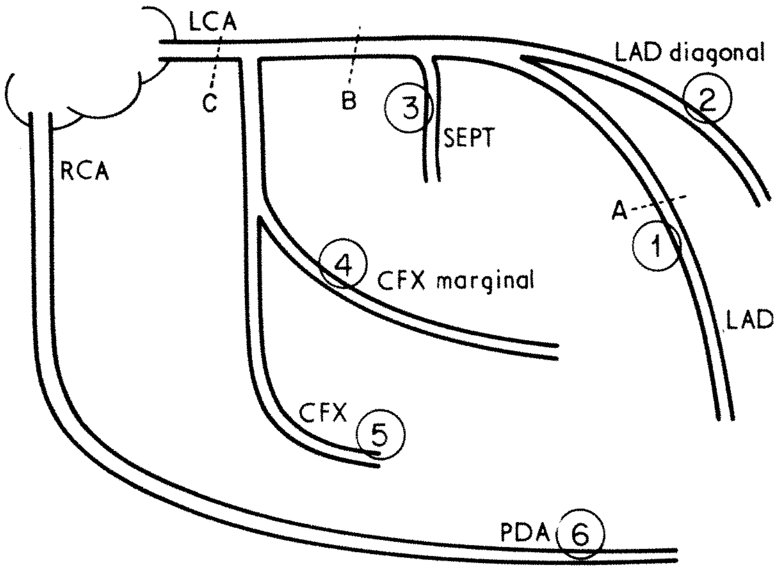

Fig. 1 *The jeopardy score system as a semiquantitative measure of extent of left ventricular involvement by coronary artery disease. The coronary circulation is considered as six arterial segments as numbered in the figure. Each segment involved, directly or indirectly (by a lesion proximal to its origin), counts two points. For example, lesions located at points A, B, or C in the figure would give jeopardy scores of 2, 6, and 10, respectively. Also see text. RCA, right coronary artery; LCA, left coronary artery; LAD diagonal, major diagonal branch of left anterior descending artery; SEPT, major septal perforating artery; LAD, left anterior descending artery beyond the major diagonal and septal branches; CFX marginal, major marginal branch of the left circumflex artery; CFX, left circumflex artery beyond the major marginal branch; PDA, posterior descending coronary artery.*

observations compared with the initial observations averaged 0·02 (range 0·00 to 0·06).

For purposes of this study the coronary circulation was divided into 6 arterial segments. The arteriograms were assigned an arteriographic score, which we have called the 'jeopardy score', designed to express the number of segments jeopardised by significant proximal stenoses. The term 'proximal' is defined as that part of the coronary artery large enough to be bypassed by a venous bypass graft. By 'distal' is meant smaller than a size potentially able to accept connection of a venous bypass graft (estimated diameter less than 1 to 1·5 mm). An artery was considered significantly stenosed if more than 70 per cent of the estimated luminal area was obstructed. In the jeopardy score system, stenoses were not differentiated from complete occlusions (though complete occlusions were enumerated separately). Fig. 1 illustrates the 6 arterial segments and shows the principle of the jeopardy score. For example, if there had been a normal coronary arteriogram in the series, it would have been assigned a jeopardy score of zero. A patient with a lesion involving only 1 of the 6 segments was arbitrarily assigned 2 jeopardy score points. If the lesion were in a parent vessel proximal to more than 1 of the 6 designated segments, the arteriogram was assigned 2 points for each segment indirectly jeopardised. Patients with disease affecting all of the segments, either directly or indirectly, had a jeopardy score of 12 points. In patients with left coronary arterial dominance, the 2 points assigned to the posterior descending artery were considered in the circumflex system, rather than in the right coronary arterial system.

Distal disease was considered separately according to the total number of segments significantly narrowed in their distal extent. Vessels counted as being distal included arterial branches other than the 6 segments designated in the jeopardy score system as well as the distal third (approximately) of these 6 arteries.

Collateral circulation was noted, where collaterals were counted in terms of the number of sources filling other segments in retrograde fashion. For example, if the left anterior descending artery beyond a proximal occlusion filled both from branches of the circumflex artery as well as from the right coronary artery, the arteriogram was credited as showing 2 collateral sources.

DEFINITION OF CARDIOMYOPATHIC SYNDROME DUE TO CORONARY ARTERY DISEASE

We have intended this term to refer to patients with coronary disease who have heart failure caused by multiple and widespread abnormalities of left ventricular wall motion severe enough to have resulted in a significant reduction of resting left ventricular ejection fraction. All patients classified

Table 1 *Criteria for heart failure (30 patients)*

Clinical features	*No. of patients*
Symptoms of dyspnoea	24
Gallop sounds (S4 and/or S3)	26
Electrocardiographic left atrial enlargement	20
Chronic digitalis and diuretic requirements	25
Raised left ventricular end diastolic pressure at time of catheterisation*	17
Left ventricular enlargement (chest film)	20

*Post-A wave end diastolic pressure > 15 mmHg.

as having it had a left ventricular ejection fraction ≤0·48. Heart failure was defined as being present when a patient had radiological evidence of left heart failure, had had a raised mean jugular venous pressure, or had 2 of the 6 clinical features listed in Table 1. Other causes of heart failure due to coronary artery disease (see Discussion) were specifically excluded before a diagnosis of cardiomyopathy due to coronary artery disease was made.

STATISTICAL ANALYSIS

All statistical analyses were done by either the Student's t test or by χ^2 analysis with Yates' correction.

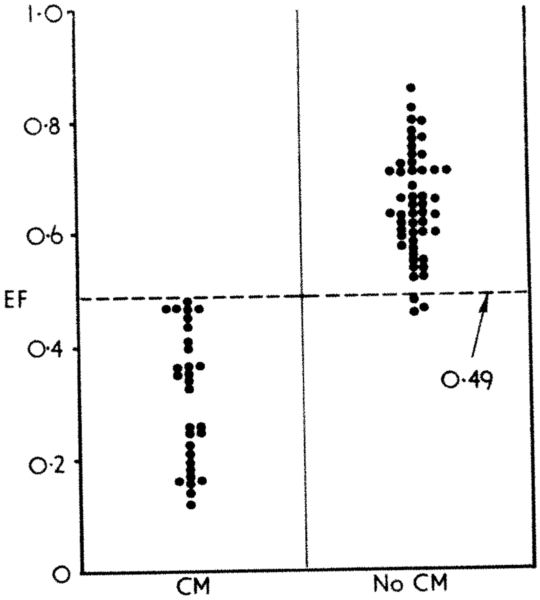

Fig. 2 *The study population is shown according to ejection fraction (EF) and presence or absence of cardiomyopathy (CM).*

Results

Of the 84 patients, 30 were classified as having the cardiomyopathic syndrome. The mean ejection fraction was 0·31 in this group and 0·63 in the group without cardiomyopathy. The highest ejection fraction encountered in a patient we believed to have clinical features related to left ventricular function impairment was 0·48. The total group of 84 patients, classified as having or not having cardiomyopathy, with 0·49 used as the 'upper cutoff' ejection fraction in the definition of cardiomyopathy, is shown in Fig. 2. Only 3 patients not classified as having cardiomyopathy had an ejection fraction below 0·48, and the lowest ejection fraction of these was 0·44; none of these patients had any of the clinical features shown in Table 1. Thus, there was very little overlap in ejection fraction between the group with cardiomyopathy compared with the group without it. This was so even though most of the patients had ventriculograms performed in only a single plane. There is, on average, a variation of 0·08 in ejection fractions calculated from single plane, compared with biplane, ventriculograms in such patients (Cohn *et al.*, 1974a).

The cardiomyopathy group included all patients in the study who at any time had had documented evidence of heart failure, as well as all patients having 2 or more of the 6 clinical stigmata of chronic heart failure shown in Table 1. There were 4 patients with isolated ventricular aneurysms, but none of these was large enough to cause the clinical features of heart failure or significant reduction in ejection fraction. There were no patients with heart failure judged to be due to relatively isolated mitral regurgitation or who had episodic pulmonary oedema thought to be secondary to recurrent, reversible ischaemia. There were no patients with rupture of the ventricular septum. One-third (10/30) of the patients with cardiomyopathy did not have increased heart size on plain chest films. This finding is in agreement with the recent study of Yatteau *et al.* (1974).

There was a much higher arteriographic jeopardy score in patients with cardiomyopathy (10·7 ±0·4)[1] compared with those without it (5·3 ±0·6) ($P < 0·01$) (Fig. 3). Every patient with cardiomyopathy had a jeopardy score of 8 or greater. Also, on average there were a larger number of completely occluded proximal vessels in patients with cardiomyopathy (1·4 ±0·2), compared with those without it (0·8 ± 0·1) ($P < 0·002$). It is of interest that each patient with cardiomyopathy who had a jeopardy score of 8 had at least one completely occluded proximal vessel, whereas 5 patients with this syndrome and

[1] Throughout the text, ± refers to standard error of the mean.

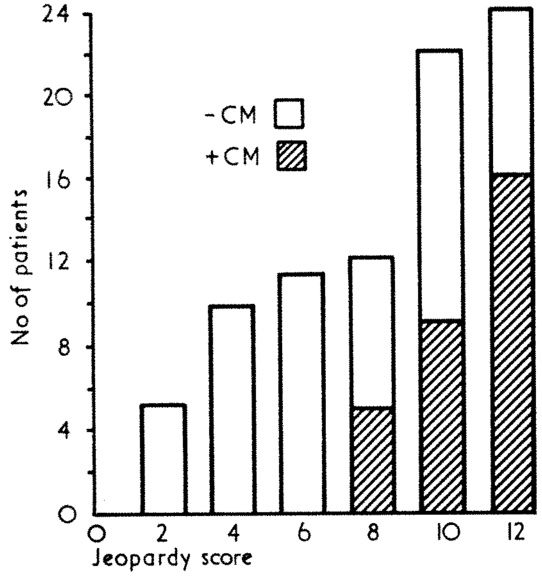

Fig. 3 *The study population shown as numbers of patients with a given jeopardy score. It can be seen that all patients with cardiomyopathy (CM) had a jeopardy score ≥8.*

a jeopardy score of 10 or 12 did not have any completely occluded vessels. Neither the presence of collateral vessels (0·8 ±0·2 vs 0·6 ±0·2 collateral sources in patients with and without cardiomyopathy), nor the extent of distal disease (0·5 ±0·2 vs 0·4 ±0·2 diseased distal vessels in patients with and without cardiomyopathy) was related to the occurrence of cardiomyopathy.

Cardiomyopathy was strongly associated with the occurrence of multiple myocardial infarcts. When transmural and non-transmural myocardial infarcts were combined, there were an average of 1·9 ±0·3 myocardial infarcts per patient in the group with cardiomyopathy and 0·9 ±0·2 myocardial infarcts per patient in the group without it. Nineteen of 30 (64%) patients with cardiomyopathy had ≥2 myocardial infarcts, whereas only 11 of 54 (20%) without it had ≥2 myocardial infarcts (P < 0·001). This finding is even more striking when transmural myocardial infarcts are considered separately; 14 of 30 (47%) patients with cardiomyopathy and only 4 of 54 (9%) without it had ≥2 transmural myocardial infarcts (P < 0·001).

Table 2 *Specificity of criteria for heart failure*

Feature	*No. of patients with feature who were counted as having heart failure* / *Total No. of patients with feature*	
Dyspnoea	24/31	0·77
Gallop sounds	26/60	0·44
Electrocardiographic left atrial enlargement	20/26	0·77
Digitalis and diuretic	25/36	0·69
End diastolic pressure	17/19	0·90
Left ventricular enlargement	20/24	0·83

Discussion

It is important when examining the correlation between clinical heart failure and angiographic data that heart failure be defined as precisely as possible. Yet in retrospective studies of the present type, just as in the practice of clinical cardiology, radiological evidence of left heart failure or clinical evidence of right heart failure is often not available in patients who are none the less appropriately considered as having had heart failure in the past. This is so because chest *x*-rays were not always done when the patient was symptomatic, because the patient improved after the institution of therapy, or because left atrial hypertension reached symptomatic levels only with effort and was not present in enough degree at rest to be evident on chest films. To counter this problem we have taken a probability approach similar to that which is taken in clinical practice. Not only were patients counted as having heart failure who had had documented radiological evidence, but also those who had a constellation of other features of varying specificity (Table 1). Of the 6 clinical features shown in Table 1, 2 were required for the diagnosis of heart failure because these features considered in isolation lack specificity. The specificity of each of these 6 features considered individually for designating a diagnosis of heart failure in the present study is shown in Table 2. Not surprisingly, raised left ventricular end diastolic pressure had the highest specificity, but the lowest sensitivity. The most sensitive feature, but by far the least specific, was the presence of gallop sounds. This relative lack of specificity was accounted for entirely by fourth heart sounds; every patient with a third heart sound was counted as having heart failure. The individual specificity of the other features ranged from 0·69 to 0·83; these values seemed acceptably high and consistent with everyday clinical experience.

All patients with evidence of heart failure in the present series of 84 patients with coronary artery disease had diffuse abnormalities of left ventricular wall motion severe enough to reduce significantly the left ventricular ejection fraction at rest, a syndrome we refer to as 'the cardiomyopathic syndrome due to coronary artery disease'. We have used this designation in part because it bears a ventriculographic resemblance to primary myocardial disease. More importantly, we wish to distinguish it from other causes of chronic heart failure in coronary artery disease: isolated ventricular aneurysm, chronic mitral regurgitation (those cases where the left ventricular ejection fraction is relatively preserved), rupture of the interventricular septum, and cases where episodic pulmonary oedema is secondary to reversible ischaemia (Brody and Criley, 1970). Distinguishing these syndromes is important not only because they may differ in their relation to the extent of coronary disease, but also because they may differ in their clinical and therapeutic implications. That the cardiomyopathic syndrome was the only cause of heart failure present in this series may have been partly fortuitous, but it also reflects the fact that it is the most common of these syndromes.

Our results show that the occurrence of cardiomyopathy is clearly related to the angiographic extent of coronary artery disease. Not only was there a highly significant difference in mean jeopardy score between patients with and without cardiomyopathy, there was also a sharp cutoff in jeopardy score (8) below which it did not occur (Fig. 3).

The same conclusion would have been reached had the 1, 2, 3-vessel disease notation been used to score the coronary arteriograms: of 15 patients with single-vessel disease, none had cardiomyopathy; of 19 patients with 2-vessel disease, 3 had it; and, of 50 patients with 3-vessel disease, 27 had it. Further analysis of these data, however, shows the jeopardy score system to be more useful than the 1, 2, 3-vessel disease notation for predicting the presence or absence of cardiomyopathy. The predictive advantage of the jeopardy score is seen mainly in the mid-range of the two systems; a jeopardy score of less than 8 predicted more patients not at risk for cardiomyopathy (26 patients) than did 1-vessel disease (15 patients), and a jeopardy score of 8 or greater was more specific for predicting the presence of cardiomyopathy (30 of 58 had it) than was 2- and 3-vessel disease (30 of 69 had it). It is to be noted that the degree of stenosis is evaluated in all-or-none fashion, i.e. judged to be haemodynamically significant or not, in both systems. In the interest of simplicity this seems justifiable since there appears from recent studies to be an element of interobserver variability in judging degree of stenosis (Zir *et al.*, 1976). The superiority of the jeopardy score is presumably because it more precisely relates the extent of coronary disease to the extent of left ventricle involved, which is accomplished by assigning values to lesions according to their location relative to major branch points of the involved artery. Saltups *et al.* (1971) have used a similar system in evaluating the electrocardiographic and haemodynamic consequences of exercise in patients with coronary artery disease.

The finding that the cardiomyopathic syndrome is specifically related to the extent of coronary disease supports the finding of Proudfit *et al.* (1968) that chronic heart failure in coronary artery disease is always associated with severe 2- or 3-vessel disease if patients with ventricular aneurysms, severe mitral regurgitation, or extracardiac causes of heart failure are excluded. The relation of clinical heart failure or its haemodynamic correlates to the angiographic extent of coronary disease has not been apparent in studies which have failed to distinguish the cardiomyopathic syndrome from other causes of chronic heart failure in coronary artery disease (Herman *et al.*, 1967; Baxley *et al.*, 1971; Cohn *et al.*, 1974b). This is explained by the fact that other heart failure syndromes are related in a less specific way to the coronary arteriogram than is cardiomyopathy due to coronary artery disease. For example, patients with ventricular aneurysms, even when the aneurysm is large, commonly have jeopardy scores of 6 and below (Lee *et al.*, 1976). Similarly, some of the patients with mitral regurgitation and heart failure in the study of Baxley *et al.* (1971) had single-vessel coronary artery disease.

Of 58 patients in the present study with jeopardy scores of 8 or more, 30 had cardiomyopathy and 28 did not. Thus, extensive coronary artery disease is necessary but not always sufficient for the development of cardiomyopathy. We do not know why some patients with high jeopardy scores develop multiple myocardial infarctions and other patients with high jeopardy scores do not. Despite more than three decades of study, beginning with the pioneering contributions of Blumgart *et al.* (1940), it is not known why the same degree of arterial obstruction results in myocardial infarction in one patient and not in another. Nevertheless, our data strongly suggest that extensive coronary disease places patients at risk for the development of cardiomyopathy by virtue of being a prerequisite to multiple myocardial infarcts. There were on average twice as many myocardial infarcts in patients with, compared with those without, cardiomyopathy. This finding is in accord with the recent study of Yatteau *et al.* (1974) and is consistent with the observation (Hamilton *et al.*, 1972; Amsterdam, 1973; Hamby *et al.*, 1974) that significant depression of the resting left ventricular ejection fraction in coronary disease virtually always implies previous infarction. It is for this reason that we prefer the designation 'cardiomyopathic syndrome due to coronary artery disease' to the designation 'ischaemic cardiomyopathy' (Burch *et al.*, 1970), which carries the connotation, inherent in the word 'ischaemia', of reversibility. It might be argued that patients with this cardiomyopathic syndrome do not invariably have infarcts which can be historically or electrocardiographically documented (Raftery *et al.*, 1969), and, in fact, this was true of 1 of the 30 patients with cardiomyopathy in the present study. It is probable, however, that all patients with cardiomyopathy have infarcts, albeit non-transmural and clinically silent in a few. The high correlation of the cardiomyopathic syndrome with multiple infarcts explains why several studies have found that such patients, at least those with the most severely impaired left ventricular function (ejection fraction less than 0·25), do not appear to benefit from revascularisation procedures (Yatteau *et al.*, 1974; Kouchoukos *et al.*, 1972).

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References

Amsterdam, E. A. (1973). Function of the hypoxic myocardium. Experimental and clinical aspects. *American Journal of Cardiology*, **32,** 461–471.

Baxley, W. A., Jones, W. B., and Dodge, H. T. (1971). Left ventricular anatomical and functional abnormalities in chronic postinfarction heart failure. *Annals of Internal Medicine*, **74,** 499–508.

Blumgart, H. L., Schlesinger, M. J., and Davis, D. (1940). Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathological findings. *American Heart Journal*, **19,** 1–91.

Brody, W., and Criley, J. M. (1970). Intermittent severe mitral regurgitation. Hemodynamic studies in a patient with recurrent acute left-sided heart failure. *New England Journal of Medicine*, **283,** 673–676.

Burch, G. E., Giles, T. D., and Colcolough, H. L. (1970). Ischemic cardiomyopathy. *American Heart Journal*, **79,** 291–292.

Cohn, P. F., Gorlin, R., Adams, D. F., Chahine, R. A., Vokonas, P. S., and Herman, M. V. (1974a). Comparison of biplane and single plane left ventriculograms in patients with coronary artery disease. *American Journal of Cardiology*, **33,** 1–6.

Cohn, P. F., Herman, M. V., and Gorlin, R. (1974b). Ventricular dysfunction in coronary artery disease. *American Journal of Cardiology*, **33,** 307–310.

Dash, H., Johnson, R. A., Dinsmore, R. E., Francis, C. K., and Harthorne, J. W. (1977). Cardiomyopathy syndrome due to coronary artery disease. II. Increased prevalence in patients with diabetes mellitus. A matched pair analysis. *British Heart Journal*, **39,** 740–747.

Hamby, R. I., Hoffman, I., Hilsenrath, J., Aintablian, A., Shanies, S., and Padmanabhan, V. S. (1974). Clinical, hemodynamic, and angiographic aspects of inferior and anterior myocardial infarctions in patients with angina pectoris. *American Journal of Cardiology*, **34,** 513–519.

Hamilton, G. W., Murray, J. A., and Kennedy, J. W. (1972). Quantitative angiocardiography in ischemic heart disease. The spectrum of abnormal left ventricular function and the role of abnormally contracting segments. *Circulation*, **45,** 1065–1080.

Herman, M. V., Heinle, R. A., Klein, M. D., and Gorlin, R. (1967). Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. *New England Journal of Medicine*, **277,** 222–232.

Kouchoukos, N. T., Doty, D. B., Buettner, L. E., and Kirklin, J. W. (1972). Treatment of postinfarction cardiac failure by myocardial excision and revascularization. *Circulation*, **45-46,** Suppl. I, 72–78.

Lee, D. C. S., Johnson, R. A., Boucher, C. B., Wexler, L. F., McEnany, M. T. (1976). Left ventricular aneurysms: an analysis of survival in operated and unoperated patients. *Circulation* (Suppl. II), 54–259.

Proudfit, W. L., Shirey, E. K., Sheldon, W. C., and Sones, F. M., Jr. (1968). Certain clinical characteristics correlated with extent of obstructive lesions demonstrated by selective cine-coronary arteriography. *Circulation*, **38,** 947–954.

Raftery, E. B., Banks, D. C., and Oram, S. (1969). Occlusive disease of the coronary arteries presenting as primary congestive cardiomyopathy. *Lancet*, **2,** 1147–1150.

Saltups, A., McCallister, B. D., Hallermann, F. J., Wallace, R. B., Smith, R. E., and Frye, R. L. (1971). Left ventricular hemodynamics in patients with coronary artery disease and in normal subjects. Correlations with the extent of coronary artery lesions and the electrocardiogram. *American Journal of Medicine*, **50,** 8–19.

Sandler, H., and Dodge, H. T. (1968). The use of single-plane angiocardiograms for the calculation of left ventricular volume in man. *American Heart Journal*, **75,** 325–334.

Yatteau, R. F., Peter, R. H., Behar, V. S., Bartel, A. G., Rosati, R. A., and Kong, Y. (1974). Ischemic cardiomyopathy. The myopathy of coronary artery disease. Natural history and results of medical versus surgical treatment. *American Journal of Cardiology*, **34,** 520–525.

Zir, L. M., Miller, S. W., Dinsmore, R. E., Gilbert, J. P., and Harthorne, J. W. (1976). Interobserver variability in coronary angiography. *Circulation*, **53,** 627–632.

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Cardiomyopathic syndrome due to coronary artery disease[1]

II: Increased prevalence in patients with diabetes mellitus: a matched pair analysis

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To test the hypothesis that the prevalence of a cardiomyopathic syndrome in association with coronary artery disease is higher among diabetic patients, clinical, ventriculographic, and arteriographic features of coronary artery disease were evaluated in 84 patients with coronary artery disease. Forty-two diabetics were compared with 42 non-diabetics who were randomly selected and matched for age, sex, blood pressure, and serum lipids. The diabetic group represented all diabetic patients with angiographic coronary artery disease identified over a 6-year period who could be matched for these variables. The coronary circulation was divided into 6 arterial segments, and arteriograms were assigned a jeopardy score that expresses the number of segments jeopardised by significant proximal stenoses. Distal coronary artery disease was scored separately. The cardiomyopathic syndrome due to coronary artery disease was defined by evidence of chronic heart failure in association with significant reduction of the left ventricular ejection fraction ($\leq 0{\cdot}48$) caused by multiple and widespread left ventricular wall motion abnormalities.

There was an increased prevalence of the syndrome in the diabetic group compared with the control group (20 patients vs 10 patients, $P<0{\cdot}05$) and this was reflected in a lower mean ejection fraction in the diabetic group as a whole (0·47 vs 0·56, $P<0{\cdot}05$). There was also a higher prevalence of multiple myocardial infarcts (21 diabetics vs 9 controls with ≥ 2 myocardial infarctions, $P<0{\cdot}05$) and anterior myocardial infarcts (23 diabetics vs 13 controls, $P<0{\cdot}05$) in the diabetic group. There were no differences between the two groups in the prevalence of stable or unstable angina, persistent arrhythmias, or intraventricular conduction defects.

The mean jeopardy score in patients with the cardiomyopathic syndrome was the same ($10{\cdot}7 \pm 0{\cdot}4$ vs $10{\cdot}6 \pm 0{\cdot}3$) whether diabetic or control. No patient, diabetic or control, with cardiomyopathy had a jeopardy score of <8. Furthermore, the relation of cardiomyopathy to multiple myocardial infarctions was as strong in the diabetic patients (15 of 20 diabetics with cardiomyopathy had had ≥ 2 myocardial infarctions, 6 of 22 diabetics without cardiomyopathy had had ≥ 2 myocardial infarctions; $P<0{\cdot}001$) as it was in the overall study population.

There was no significant difference in mean jeopardy score between diabetic and control groups as a whole ($8{\cdot}9 \pm 0{\cdot}5$ vs $8{\cdot}2 \pm 0{\cdot}5$), but an increased fraction of the diabetic subpopulation with jeopardy scores of ≥ 8 had cardiomyopathy (20 of 30) compared with the control subpopulation with jeopardy scores of ≥ 8 (10 of 28). The prevalence of completely occluded coronary arteries did not differ between diabetic and control groups. There was a higher prevalence of distal coronary artery disease in diabetic patients (24 diabetic vessels vs 10 control vessels), which was significant, or not, depending on whether correction was made for non-visualised distal vessels.

We conclude that there is an increased prevalence of the cardiomyopathic syndrome in diabetic patients with coronary artery disease, compared with non-diabetic patients with coronary artery disease, who come to angiography, and that this difference exists independently of hypertension and hyperlipidaemia. However, the cause of the cardiomyopathic syndrome, i.e. its relation to the extent of proximal coronary artery disease and to the occurrence of multiple myocardial infarcts, is the same in both diabetic and non-diabetic patients.

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Diabetes mellitus is generally accepted to be an important risk factor for the development of premature coronary artery disease (Stearns, *et al.*, 1947; Liebow *et al.*, 1964; Ostrander *et al.*, 1965). It has been speculated that not only the incidence, but also the severity, of coronary artery disease is increased in diabetics (Badger and Liebow, 1965; Partamian and Bradley, 1965). It is not known whether diabetic patients with coronary artery disease differ from non-diabetics with coronary artery disease in clinical manifestations, angiographic anatomy, or extent of left ventricular function impairment. It has been our clinical impression, and that of others (Ryan *et al.*, 1972), that coronary artery disease in diabetics is more likely to be complicated by the development of a cardiomyopathic syndrome than is coronary artery disease in non-diabetic patients. This issue is complicated however, by the recent postulate (Rubler *et al.*, 1972; Kannel *et al.*, 1974; Regan *et al.*, 1974) that there may be a form of cardiomyopathy in patients with diabetes which is unrelated to coronary artery disease. The present study was undertaken to evaluate clinical, ventriculographic, and arteriographic features in 84 patients with coronary artery disease—42 diabetics compared with 42 randomly selected matched controls. In particular, this study is designed to test the hypothesis that the prevalence of a cardiomyopathic syndrome in association with coronary artery disease is higher among the diabetic patients. Furthermore, the present study examines whether the cause of the cardiomyopathic syndrome in diabetic patients with coronary artery disease is the same as the cause of cardiomyopathic syndrome in non-diabetic patients with coronary disease. For this reason the relations between the presence of cardiomyopathic syndrome, the extent of angiographic coronary disease, and the prevalence of myocardial infarction are analysed in the two groups of patients.

Methods

The study population consists of 42 matched pairs of diabetic and control patients with coronary artery disease. All patients admitted to the Massachusetts General Hospital between January 1968 and December 1973 who underwent coronary angiography were eligible for the study. Patients without significant coronary artery disease and patients with other types of heart disease were excluded.

Patients were considered to have diabetes mellitus if one of the following criteria were present: a fasting whole blood glucose $\geq 6{\cdot}1$ mmol/litre (110 mg/100 ml); in those patients with a positive family history for diabetes, a 2-hour postprandial blood glucose $\geq 8{\cdot}3$ mmol/litre (150mg/100ml); or, in those patients with a negative family history for diabetes, a 2-hour postprandial blood glucose $\geq 11{\cdot}1$ mmol/litre (200 mg/100 ml). Patients were excluded if the raised blood sugars were measured during a stressful state or while they were taking a diabetogenic drug. The absence of diabetes was defined as a 2-hour postprandial blood glucose $< 6{\cdot}7$ mmol/litre (120 mg/100 ml), and, when available, a fasting blood glucose $< 5{\cdot}6$ mmol/litre (100 mg/100 ml). No patient with a positive family history for diabetes was accepted as a member of the control series. Whole blood glucose was determined by the ferric cyanide reduction method. These criteria are necessarily arbitrary and were designed to select a population which was definitely diabetic to compare with a population definitely non-diabetic, thus avoiding the ambiguity of borderline carbohydrate intolerance. Not only was the presence of 'chemical' diabetes (Williams and Porte, 1974) required, but also evidence of either 'genetic' diabetes or severe carbohydrate intolerance.

The subject population was selected from the computer files of patient diagnoses at the Massachusetts General Hospital. Patients with the diagnosis of 'diabetes mellitus' and 'coronary angiography' were identified and screened. Potential candidates for the control group were selected randomly from the computer files according to the diagnosis of 'coronary angiography'. Of 609 potential control patients 214 were excluded because there was no record of a postprandial blood glucose or of the family history as it pertained to diabetes, and 285 were excluded because they had either a positive family history for diabetes or raised blood glucose levels, but otherwise did not meet the criteria for inclusion as diabetics. Of the total number of patients screened, diabetes was confirmed in 56 patients and the absence of diabetes was confirmed in 110.

For each patient an average blood pressure was calculated on the basis of the initial and prevailing pressures during one or more hospital admissions, as well as any known past history of hypertension. In cases where there was more than one pair of lipid determinations, the values were averaged. Non-fasting measurements and lipid values drawn at the time of acute myocardial infarction were excluded. Each diabetic subject was individually and randomly matched with a member of the pool of control patients on the basis of age, sex, systolic, and diastolic blood pressure, serum cholesterol, and serum triglycerides. The maximal age difference was 10 years. The maximal difference in serum cholesterol was 2·4 mmol/litre, and in serum triglycerides

1·1 mmol/litre. Suitable controls could not be found for 14 diabetic patients, leaving 42 matched pairs which comprise the study population.

Each patient's medical record was examined for pertinent historical and clinical data. Angina pectoris was divided into two major categories: stable and unstable angina. Criteria used for the diagnosis of unstable angina were prolonged chest pain leading to hospital admission (without myocardial enzyme rises in serum or the development of Q waves on the electrocardiogram), the new onset of rest or nocturnal chest pain, and, when occurring over a period of less than 2 months, an increase in the frequency and severity of effort angina.

Persistent arrhythmias, atrioventricular conduction defects, bundle-branch blocks, fascicular blocks, and nonspecific interventricular conduction defects were enumerated.

Myocardial infarcts were defined as transmural or non-transmural. The former were diagnosed only in the presence of electrocardiographic Q waves of at least 0·04 s in duration, or, if Q waves were equivocal, akinesis or dyskinesis of the appropriate segment of the left ventriculogram and a typical history. Non-transmural infarcts were diagnosed when typical serum enzyme changes were unaccompanied by the evolution of Q waves. Electrocardiographic left atrial enlargement was defined as terminal P wave negativity in lead V1 exceeding 0·03 mm/s.

The assessment of selective coronary arteriograms, left ventriculograms, and plain chest films in this patient population has been described in a companion paper (Dash *et al.*, 1977). All angiograms and *x*-rays were viewed by one of us (R.E.D.) without knowledge of the clinical status of the patient. Eighty-one patients had cineventriculograms (right anterior oblique in 78, biplane in 3) from which left ventricular volumes were calculated by the modified area-length method, using outlines drawn from estimated end diastolic and end systolic cine frames. Left ventricular ejection fraction was calculated for each by dividing left ventricular stroke volume by left ventricular end diastolic volume.

'Cardiomyopathic syndrome due to coronary artery disease' is a name we have applied to patients with multiple and widespread left ventricular wall motion abnormalities leading to significant reduction in the resting left ventricular ejection fraction and evidence of chronic heart failure. The purpose of this name is to distinguish cardiomyopathy resulting from coronary artery disease from other causes of chronic heart failure in coronary artery disease (isolated ventricular aneurysm, chronic and relatively isolated mitral regurgitation, rupture of the interventricular septum, and cases where episodic pulmonary oedema is secondary to reversible ischaemia). All patients diagnosed as having cardiomyopathy had a left ventricular ejection fraction $\leq 0{\cdot}48$ and clinical features consistent with chronic heart failure. Patients were considered as having evidence of chronic heart failure if they had had definite radiological evidence of left heart failure, had had raised mean jugular venous pressure, or had 2 of the 6 clinical features listed in Table 1 in Paper I (Dash *et al.*, 1977). Only 3 patients not classified as having cardiomyopathy had an ejection fraction below 0·48 (the lowest of these was 0·44), and none of these 3 had any of the criteria for heart failure.

The extent of proximal coronary artery disease was scored by the angiographic 'jeopardy score' system which has been described in detail previously by Dash *et al.* (1977). This system assigns value to significant coronary lesions (greater than 70% estimated luminal area reduction) according to their location relative to major branch points of the involved artery. The coronary circulation is considered as 6 arterial segments (right coronary artery, 1 segment; left anterior descending coronary artery, 3 segments; left circumflex coronary artery, 2 segments) and 2 points are assigned for each segment jeopardised, directly or indirectly, by significant proximal stenosis. For example, had there been a normal coronary arteriogram in the present series, it would have been assigned a jeopardy score of zero; patients with disease affecting all of the segments had a jeopardy score of 12. The 2 points assigned to the right coronary artery (posterior descending artery) were considered in the circumflex system if there was left coronary arterial dominance.

Distal coronary artery disease was assessed by adding the number of arterial segments significantly narrowed in their distal extent. By 'distal' is meant smaller than a size able to accept connection of a venous bypass graft (less than 1 to 1·5 mm). Vessels counted as being distal included arterial branches other than the 6 segments designated in the jeopardy score system as well as the distal third (approximately) of these 6 arteries. Some distal vessels were either poorly opacified or not visualised because of proximal stenosis or occlusion. For this reason the following adjustment was made in order to accomplish comparative analysis of diabetics and controls: in each matched pair of patients in which a distal vessel was poorly visualised the corresponding artery in the paired arteriogram was eliminated from the analysis. This was done for 8 vessels in the diabetic group and 3 vessels in the control group.

Matched-pair statistical analyses were done by the paired Student's t test. Analyses not involving

Table 1 *Comparison of matched characteristics in diabetic and control groups*

Matched characteristic	*Diabetic*	*Control*
Age (y)	54 ±1*	54 ±1
Systolic blood pressure (mmHg)	133 ±3	133 ±2
Diastolic blood pressure (mmHg)	81 ±2	82 ±2
Serum cholesterol (mmol/litre)	6·5 ±0·2 (249 ±9 mg/100 ml)	6·4 ±0·2 (246 ±9 mg/100 ml)
Serum triglycerides (mmol/litre)	2·1 ±0·3 (188 ±23 mg/100 ml)	2·1 ±0·1 (185 ±12 mg/100 ml)

*In all tables and throughout the text ± refers to standard error of the mean.

comparison of the diabetic and control patients on a matched-pair basis were performed either by the Student's t test or by χ^2 analysis with Yates' correction.

Results

The matching process for age, blood pressure, and serum lipids was successful; the similarity in group means for these variables, comparing diabetics with controls, is shown in Table 1. Analysis of risk factors that were not specifically matched showed no significant differences between the two groups for past history of smoking, family history for premature coronary artery disease, the presence of left ventricular hypertrophy on electrocardiogram (Sokolow and Lyon, 1949), or the prevalence of alcoholism. Diabetics tended to have a higher prevalence of obesity (15 diabetics, 7 controls), but the difference was not statistically significant. Obesity was defined according to the percentage of ideal body weight (Metropolitan Life Insurance Company, *Statistical Bulletin* 1959). Of the 42 diabetics, 29 had symptoms referable to their diabetes and 13 were asymptomatic patients with chemical diabetes. Thirty-two diabetics had raised fasting blood glucose values and 16 required insulin. Only one patient had diabetes of juvenile onset.

There were no differences between diabetic and control groups in the prevalence of stable or unstable angina, persistent arrhythmias, or intraventricular conduction defects (Table 2). Approximately 75 per cent of the patients in each group developed unstable angina at some point in their clinical course. Though the prevalence of ventricular aneurysm was higher in the control group, the numbers are too small for statistical analysis.

There were a total of 59 myocardial infarcts (transmural and non-transmural) in the diabetic patients and 45 myocardial infarcts in the control group; this difference is not significant. The prevalence of transmural myocardial infarcts also did not differ in the two groups (44 in diabetics, 33 in controls). However, there was a significantly increased prevalence of multiple myocardial infarcts in diabetics (21 diabetics and 9 controls with ≥ 2 myocardial infarcts, $P < 0{\cdot}05$). This is also true if multiple transmural myocardial infarcts are considered separately (14 diabetics and 4 controls with ≥ 2 transmural myocardial infarcts). Diabetic patients also had a significantly higher prevalence of anterior myocardial infarcts (23 in diabetics, 13 in controls, $P < 0{\cdot}05$).

Table 3 shows the number of patients with cardiomyopathy in each group. Of the 42 diabetic patients 20 had cardiomyopathy whereas only 10 controls had this syndrome ($P < 0{\cdot}05$). The higher prevalence of cardiomyopathy among diabetic patients is reflected in the mean left ventricular ejection fraction of the diabetic group (0·47), which is significantly lower than that of the control group (0·56) ($P < 0{\cdot}05$). The fraction of patients with cardiomyopathy who had cardiomegaly on plain chest films was similar in diabetics and controls (14/20 diabetic patients and 6/10 control patients).

It has previously been shown that in this population of patients as a whole there is a higher jeopardy score in the patients with cardiomyopathy compared with those without it (Dash *et al.*, 1977).

Table 2 *Frequency of coronary artery disease syndromes*

Syndrome	*No. of patients*	
	Diabetic	*Control*
Stable angina of effort	35	39
Stable angina at rest	14	19
Unstable angina	30	32
Recurrent unstable angina	16	15
Persistent arrhythmias	5	2
Intraventricular conduction defects	16	11
Ventricular aneurysms	0	4

Table 3 *Prevalence of cardiomyopathy due to coronary artery disease in diabetics and controls*

	Diabetic No. of patients	*Mean EF**	*Control No. of patients*	*Mean EF**
Patients with cardiomyopathy	20†	0·29	10†	0·35
Patients without cardiomyopathy	22	0·64	32	0·62
Total	42	0·47†	42	0·56†

*EF, ejection fraction; †$P < 0{\cdot}05$, comparison of diabetic with control groups.

Table 4 *Jeopardy score in relation to cardiomyopathy in association with coronary artery disease (CM)*

	Patients with CM	*Patients without CM*	*P*
Diabetic	10·7 ±0·4	5·2 ±0·2	< 0·001
Control	10·6 ±0·3	5·4 ±0·6	< 0·01

Table 4 shows that this was equally true of diabetic and control patients.

In both the diabetic and the control group there was a tendency for cardiomyopathy to be associated with multiple myocardial infarcts (1·9 ±0·2 and 1·7 ±0·4 myocardial infarcts per patient in diabetics and controls with cardiomyopathy, respectively, and 0·9 ±0·2 and 0·9 ±0·1 myocardial infarcts per patient in diabetics and controls without cardiomyopathy, respectively). The higher prevalence of patients who had had multiple myocardial infarcts among those with cardiomyopathy reached significance in the diabetic group (15 of 20 with cardiomyopathy had ≥ 2 myocardial infarctions, 6 of 22 without cardiomyopathy had ≥ 2 myocardial infarctions, P < 0·01), but the number of control patients with cardiomyopathy was too small to allow analysis by the χ^2 test (4 of 10 controls with cardiomyopathy had ≥ 2 myocardial infarctions, 5 of 32 controls without cardiomyopathy had ≥ 2 myocardial infarctions).

The figure shows the study population divided into diabetic and control groups so that the distribution of jeopardy scores and the distribution of the cardiomyopathic syndrome relative to jeopardy score may be compared in the two groups. Cardiomyopathy occurred only in patients with jeopardy scores of 8 or greater. The mean arteriographic jeopardy score did not significantly differ between diabetic and control groups as a whole (8·9 ±0·5 versus 8·2 ±0·5). Also, considering only the subpopulation at risk for the occurrence of cardiomyopathy (jeopardy score 8 or more), there are about the same number of diabetics and controls. Within this subpopulation, however, a larger fraction of the diabetics compared with controls had cardiomyopathy (20 of 30, compared with 10 of 28) (P < 0·02) and multiple myocardial infarcts (17 of 30 versus 7 of 28) (P < 0·02).

There was no difference in the number of completely occluded vessels between diabetics and controls (1·1 ±0·2 versus 0·9 ±0·1 vessels per patient). In addition, the prevalence of collaterals did not differ between the two groups (0·7 ±0·1 versus 0·6 ±0·1 collateral sources in diabetics and controls).

Using the method of cancelling the corresponding vessel in the matched patient when the distal extent of a vessel could not be visualised (see Methods), there was a higher prevalence of diseased distal vessels in diabetic patients (24 vessels in the diabetic group, 10 in the control group; P < 0·05). However, this method introduces potential bias because more diabetic vessels could not be seen distally than in controls, hence more control vessels were cancelled. If the total number of visualised diseased distal vessels are counted in the two groups and no adjustment is made for non-visualised vessels, diabetics tended to have a higher prevalence (27 versus 18 diseased distal vessels) than controls, but the

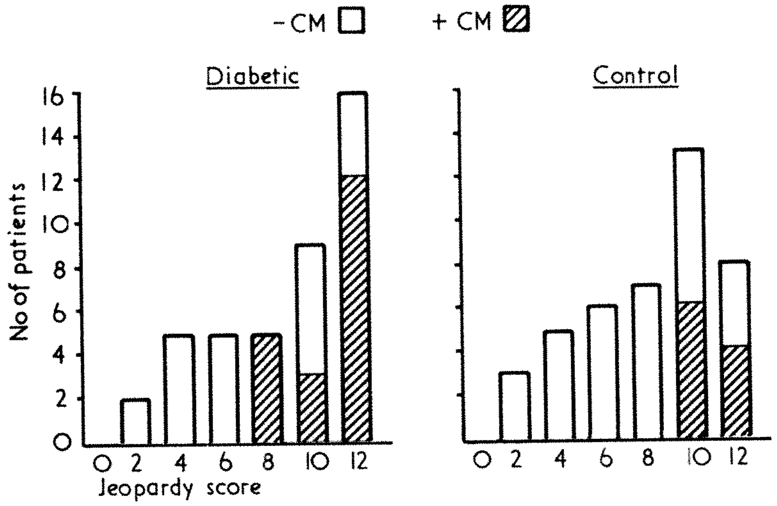

Figure *Jeopardy score histograms for diabetic and control groups. Note that the distribution of jeopardy scores is approximately the same in diabetics and controls, but that a larger fraction of the angiographic subpopulation with jeopardy score ≥ 8 had the cardiomyopathic syndrome in the diabetic group.*

Table 5 *Number of diseased distal segments per patient*

	Diabetic	*Control*
Patients with cardiomyopathy	0·6 ±0·2	0·3 ±0·2
Patients without cardiomyopathy	0·6 ±0·2	0·2 ±0·1

difference was not statistically significant. There was no relation of distal disease to cardiomyopathy in either diabetics or controls, even when adjustment was made for non-visualised vessels (Table 5).

There were no differences in the frequency of use of oral hypoglycaemic agents or insulin in diabetic patients with and without cardiomyopathy.

Discussion

Patients with diabetes mellitus have a higher incidence of hyperlipidaemia than occurs in the general population. Consequently, a study measuring the effect of diabetes on manifestations of coronary artery disease must have controls matched for serum lipids, as it is well known that lipid disorders are risk factors for premature coronary artery disease. The same is true of hypertension, since some studies have found diabetics to have raised blood pressure more frequently than non-diabetics (Pell and D'Alonzo, 1967). The present study is a comparison of two groups of patients with coronary disease, one diabetic and one non-diabetic, individually matched for age, sex, blood pressure, and serum lipids. The results show that in the patients with coronary artery disease who come to angiography at our institution there is an increased prevalence of a cardiomyopathic syndrome due to coronary artery disease, anterior myocardial infarction, and multiple myocardial infarcts in diabetic patients.

It is uncertain whether the findings of this study would extend to all diabetic patients with coronary artery disease, including those who do not undergo angiography. Conceivably, bias exists in the referral for angiography of diabetic patients compared with the referral of non-diabetic patients. However, the similarity of diabetic and control groups in the present study for the prevalence of stable and unstable angina makes the existence of a referral bias unlikely. It appears probable that the diabetics in this study are no less representative of diabetics with coronary artery disease at large than patients with coronary artery disease who undergo angiography are representative of patients with coronary artery disease in general. The degree to which the latter is the case is unknown.

This is a retrospective study even though a matched control group is used. The process of individually matching two groups of patients with coronary artery disease for each of several risk factors involves a series of approximations; it is not possible to find pairs of patients who share quantitatively identical values for all of these factors. Even so, the striking similarity in group mean values for the matched characteristics (Table 1) makes it very likely that differences found between the two groups are attributable to the presence or absence of diabetes and that they exist independently of hypertension or hyperlipidaemia.

The increased prevalence of anterior myocardial infarcts and of multiple myocardial infarcts among diabetic patients is related to their increased prevalence of cardiomyopathy. It has been shown previously that depression of the left ventricular ejection fraction in patients with coronary artery disease is related to the extent of wall motion abnormality (Hamilton *et al.*, 1972; Feild *et al.*, 1972). In general, the extent of wall motion abnormality is greater for anterior than for inferior myocardial infarction (Amsterdam, 1973; Hamby *et al.*, 1974; Lewis *et al.*, 1974). Since significant depression of the resting left ventricular ejection fraction is one of the defining features of the cardiomyopathic syndrome, it is not surprising that the prevalence of both anterior and multiple myocardial infarcts would be higher in a population with an increased prevalence of the syndrome. This line of reasoning assumes that the cause of the cardiomyopathy is the same in both diabetics and non-diabetics; that this is so is directly supported by the finding that cardiomyopathy was specifically related to the extent of proximal coronary disease, as expressed by the jeopardy score, in both diabetic and control patients. In addition, the association between cardiomyopathy and multiple myocardial infarcts, which has been shown elsewhere for the total study population (Dash *et al.*, 1977), was shown here to apply to the diabetic patients considered as a subpopulation.

Even though a high jeopardy score (8 or greater) was prerequisite for the occurrence of cardiomyopathy in both diabetics and controls, the increased prevalence of cardiomyopathy in diabetic patients did not occur because of an increased prevalence of high jeopardy scores in diabetics. There was no significant difference in mean jeopardy score between diabetic and control groups as a whole. However, an increased fraction of the diabetic subpopulation with high jeopardy scores developed cardiomyopathy compared with the control subpopulation with high jeopardy scores. There are two possible explanations for this finding—both are based on the thesis that extensive coronary artery disease is simply a requisite condition for the occurrence of multiple myocardial infarcts, which, in turn, is the cause of the cardiomyopathic syndrome (Dash *et al.*, 1977). First, if the degree of atherosclerotic narrowing of large coronary vessels were more severe in diabetic patients than in control patients, infarction would be more likely to occur in the diabetic patients. The degree of arterial narrowing would be imprecisely reflected in the jeopardy score, since this score only requires that a lesion be angiographically 'significant' to be counted. But the prevalence of completely occluded vessels did not differ between diabetic and control groups. Thus, a second explanation is perhaps more likely—that diabetic patients may be more prone to infarction than non-diabetic patients with the same degree of coronary arterial narrowing.

The results also suggest that the prevalence of distal coronary disease may be increased in diabetic patients generally. Reservation must be exercised in drawing this conclusion from our data, however. In order to compare diabetic and control pairs, it was necessary to 'cancel' vessels from consideration where the corresponding vessel in the matched patient was occluded or imperfectly visualised in its distal extent. As mentioned, it is possible that bias was introduced by this procedure. Other studies of the prevalence of distal disease in patients with diabetes have provided conflicting results (Chychota *et al.*, 1973; Verska and Walker, 1975). Whether or not distal disease is more prevalent in diabetic patients, this study shows that distal disease is not related to the presence or absence of cardiomyopathy (Table 5).

In conclusion, the results of the present study show that the prevalence of the cardiomyopathic syndrome is increased in diabetic patients with coronary artery disease who come to angiography, and that the difference is not the result of serum lipid or blood pressure abnormalities sometimes associated with diabetes mellitus. Recent reports (Rubler *et al.*, 1972; Kannel *et al.*, 1974; Regan *et al.*, 1974) have postulated the existence of a cardiomyopathy in diabetics that is not the result of coronary disease. This study does not address itself to such an entity, since all of the patients had coronary artery disease by design. However, these results strongly suggest that cardiomyopathy in most diabetic patients who have had some manifestation of coronary artery disease is the result of large vessel, proximal coronary disease. Explanatory factors independent of proximal coronary disease (distal disease, 'small-vessel' disease within the myocardium, metabolic factors, 'diabetic cardiomyopathy' unrelated to coronary disease) need not be invoked. This was shown by the finding that the angiographic extent of coronary disease was the same in diabetic and control patients with cardiomyopathy and by the finding that cardiomyopathy was related to the occurrence of multiple myocardial infarctions in diabetic patients. The increased prevalence of cardiomyopathy in diabetics occurred because a larger fraction of the angiographic subpopulation with extensive coronary disease had suffered multiple infarcts in the diabetic group, not because the number of patients with extensive coronary disease was increased. While the reason for this latter finding remains to be elucidated, it is possible that diabetics are more prone to myocardial infarction than non-diabetics with the same degree of coronary artery stenosis.

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References

Amsterdam, E. A. (1973). Function of the hypoxic myocardium. Experimental and clinical aspects. *American Journal of Cardiology*, **32**, 461–471.

Badger, G. F., and Liebow, I. M. (1965). Myocardial infarction in the practices of a group of private physicians—a comparison of patients with and without diabetes. II. The first two years, and a discussion of methodology. *Journal of Chronic Diseases*, **18**, 973–984.

Chychota, N. N., Gau, G. T., Pluth, J. R., Wallace, R. B., and Danielson, G. K. (1973). Myocardial revascularization. Comparison of operability and surgical results in diabetic and non-diabetic patients. *Journal of Thoracic and Cardiovascular Surgery*, **65**, 856–862.

Dash, H., Johnson, R. A., Dinsmore, R. E., and Harthorne, J. W. (1977). Cardiomyopathic syndrome due to coronary artery disease. I. Relation to angiographic extent of coronary disease and to remote myocardial infarction. *British Heart Journal*, **39**, 733–739.

Feild, B. J., Russell, R. O., Jr., Dowling, J. T., and Rackley, C. E. (1972). Regional left ventricular performance in the year following myocardial infarction. *Circulation*, **46**, 679–689.

Hamby, R. I., Hoffman, I., Hilsenrath, J., Aintablian, A., Shanies, S., and Padmanabhan, V. S. (1974). Clinical, hemodynamic and angiographic aspects of inferior and anterior myocardial infarctions in patients with angina pectoris. *American Journal of Cardiology*, **34**, 513–519.

Hamilton, G. W., Murray, J. A., and Kennedy, J. W. (1972). Quantitative angiocardiography in ischemic heart disease. The spectrum of abnormal left ventricular function and role of abnormally contracting segments. *Circulation*, **45**, 1065–1080.

Kannel, W. B., Hjortland, M., and Castelli, W. P. (1974). Role of diabetes in congestive heart failure: The Framingham study. *American Journal of Cardiology*, **34**, 29–34.

Lewis, B. S., Bakst, A., and Gotsman, M. S. (1974). Relationship between regional ventricular asynergy and the anatomic lesion in coronary artery disease. *American Heart Journal*, **88**, 211–218.

Liebow, I. M., Newill, V. A., and Oseasohn, R. (1964). Incidence of ischemic heart disease in a group of diabetic women. *American Journal of the Medical Sciences,* **248,** 403–407.

Metropolitan Life Insurance Company, New York. Statistical Bulletin (1959). New weight standards for men and women. **40,** 1.

Ostrander, L. D., Jr., Francis, T., Jr., Hayner, N. S., Kjelsberg, M. O., and Epstein, F. H. (1965). The relationship of cardiovascular disease to hyperglycemia. *Annals of Internal Medicine,* **62,** 1188–1198.

Partamian, J. O., and Bradley, R. F. (1965). Acute myocardial infarction in 258 cases of diabetes. Immediate mortality and five-year survival. *New England Journal of Medicine,* **273,** 455–461.

Pell, S., and D'Alonzo, C. A. (1967). Some aspects of hypertension in diabetes mellitus. *Journal of the American Medical Association,* **202,** 104–110.

Regan, T. J., Jaferi, G. A., Ahmed, S. S., Levinson, G. E., Oldewurtel, H. A., and Lyons, M. M. (1974). Cardiomyopathy in diabetes mellitus (abstract). *Circulation,* **49-50,** Suppl. III, 129.

Rubler, S., Dlugash, J., Yuceoglu, Y. Z., Kumral, T., Branwood, A. W., and Grishman, A. (1972). New type of cardiomyopathy associated with diabetic glomerulosclerosis. *American Journal of Cardiology,* **30,** 595–602.

Ryan, T. J., Flessas, A., Kowsari, M., Keefe, J., and Klein, M. (1972). The cardiomyopathy syndrome of coronary heart disease (abstract). *Circulation,* **45-46,** Suppl. II, 62.

Sokolow, M., and Lyon, T. P. (1949). The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *American Heart Journal,* **37,** 161–186.

Stearns, S., Schlesinger, M. J., and Rudy, A. (1947). Incidence and clinical significance of coronary artery disease in diabetes mellitus. *Archives of Internal Medicine,* **80,** 463–474.

Verska, J. J., and Walker, W. J. (1975). Aortocoronary bypass in the diabetic patient. *American Journal of Cardiology,* **35,** 774–777.

Williams, R. H., and Porte, D., Jr. (1974). The pancreas. In *Textbook of Endocrinology,* 5th ed., p. 502. Ed. by R. H. Williams. W. B. Saunders, Philadelphia.

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Effects of glucose and glucose-insulin-potassium on haemodynamics and enzyme release after acute myocardial infarction

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The effects on haemodynamics and infarct size (measured by total creatine kinase release) of intravenous infusions of normal saline, glucose, or glucose-insulin-potassium were studied in 36 patients with transmural acute myocardial infarction of less than 12 hours' duration. In 12 patients, 2 ml/kg 50 per cent glucose (5·55 mmol/kg) was given over 10 minutes with 0·4 unit/kg soluble insulin 5 minutes later, followed by an infusion of 1·5 ml/kg per hr of 50 per cent glucose (4·2 mmol/kg per hr) containing 0·3 unit/kg insulin and 0·15 mmol/kg potassium chloride. Similar volumes of 50 per cent glucose alone or normal saline alone were administered to 9 and 15 patients, respectively. Cardiac output and right heart pressures were measured in 28 patients by Swann-Ganz thermodilution catheter, and arterial pressure by an indwelling plastic cannula. Calculation of total enzyme release from serial creatine kinase measurements was made using individualised figures for the enzyme degradation rate.

Saline infusion had no significant effect on cardiovascular haemodynamics. Glucose did not affect heart rate, but increased mean arterial pressure and pulmonary artery diastolic pressure by 18 per cent ($P<0·001$) and 42 per cent ($P<0·001$) at 30 minutes and by 14 per cent ($P<0·005$) and 25 per cent ($P<0·005$) at 60 minutes after infusion, respectively. Glucose-insulin-potassium increased heart rate (+13%; $P<0·05$), mean arterial pressure (+15%; $P<0·01$), and pulmonary artery diastolic pressure (+27%; $P<0·005$) at 30 minutes but not at 60 minutes. Glucose increased cardiac index 22 per cent ($P<0·05$) at 60 minutes; glucose-insulin-potassium increased cardiac index by 26 per cent ($P<0·005$) at 30 minutes and by 22 per cent ($P<0·001$) at 60 minutes. There was no effect on systemic vascular resistance, but glucose and glucose-insulin-potassium enhanced left ventricular stroke work index by 17 per cent ($P<0·02$) and 25 per cent ($P<0·02$) at 30 minutes and by 27 per cent ($P<0·02$) and 22 per cent ($P<0·005$) at 60 minutes, respectively. The degree of improvement in haemodynamic functions induced by glucose and glucose-insulin-potassium were comparable. Though the data are limited, these changes were not associated with a favourable trend in enzyme release. Furthermore, in the glucose-insulin-potassium group, one patient died and another was successfully resuscitated from cardiac arrest; 2 patients died in the glucose group, while no serious complications occurred among patients in the saline group.

It was concluded that the improvement in haemodynamic functions produced by glucose and glucose-insulin-potassium infusions in uncomplicated myocardial infarcts was not associated with an obvious beneficial effect on clinical status and infarct size assessed by enzyme release. Continuation of the trial was, therefore, not ethically justifiable.

In recent years, increasing attention has been focused on the possibility that myocardial damage after acute coronary occlusion might be reduced by metabolic or pharmacological interventions. The use of glucose and glucose-insulin-potassium infusions is of particular interest on theoretical grounds. Whereas the normal heart muscle derives most of its energy from aerobic metabolism of free fatty acids (Ballard *et al.*, 1960; Evans, 1964), anaerobic breakdown of glucose becomes the main

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source of energy in myocardial ischaemia (Morgan *et al.*, 1961; Weissler *et al.*, 1968). Provision of increased quantities of glucose (or reduced quantities of free fatty acids) to the ischaemic myocardium may thus promote anaerobic glycolysis and lead to enhanced myocardial function and survival (De Leiris *et al.*, 1975). Infusions of glucose and glucose-insulin-potassium have been reported to reduce infarct size in dogs (Maroko *et al.*, 1972), and to improve myocardial function in clinical as well as experimental studies (Austen *et al.*, 1965; Majid *et al.*, 1972). Though there have been trials of glucose-insulin-potassium in the prophylaxis of cardiac arrhythmias after acute myocardial infarction in man (Mittra, 1965; Sodi-Pollares *et al.*, 1966; M.R.C. Working Party Report, 1968), the effects of this regimen on cardiac function and myocardial ischaemic damage in this clinical setting are still not clearly defined. We have, therefore, investigated the effects of glucose-insulin-potassium, glucose, and normal saline infusions on myocardial function and enzyme release in three comparable groups of patients admitted to the coronary care unit (CCU) with acute myocardial infarction.

Subjects and methods

PATIENT SELECTION

The purpose and details of the study were explained to all patients and their consent obtained. All patients studied had transmural myocardial infarcts judged on clinical features and confirmed by the presence of pathological Q waves and/or ST segment elevation in the electrocardiogram. Patients with maximum chest pain lasting longer than 12 hours, valvular heart disease, cardiogenic shock, diabetes mellitus, cardiac arrhythmias apart from isolated ectopic beats, or heart failure as indicated by ventricular gallop, basilar râles, or interstitial oedema radiologically, were excluded. Cardiac stimulants or diuretics were not required in any patient during haemodynamic study. Thirty-six patients were considered suitable for admission into the trial and were randomised into 3 groups: 12 patients received glucose-insulin-potassium infusion; 9, 50 per cent glucose; and 15 had normal saline. The 3 groups were comparable with regard to age and sex (Table 1). The mean time from the onset of maximal symptoms to therapeutic intervention was similar in the 3 groups (approximately 8 hours, Table 1), but varied widely, from 4 to 14 hours, in individual cases.

HAEMODYNAMIC MEASUREMENTS

After admission, each subject had a chest *x*-ray, and a polyethylene cannula was inserted percutaneously into a vein in the left arm for intravenous infusion and for withdrawal of blood for estimation of myocardial infarct size by serial determinations of creatine kinase (CK) activity (Sobel *et al.*, 1972; Norris *et al.*, 1975). Haemodynamic measurements were made in 28 patients under aseptic conditions in a specially equipped room in the CCU. Diazepam, 5 to 10 mg intravenously, was given on one occasion to all patients about 1 hour before haemodynamic measurements. The 8 other patients who were studied after completion of the haemodynamic trial had serial enzyme measurements only. For the haemodynamic studies an incision was made in the right antecubital fossa, and the brachial artery and a superficial cubital vein were isolated. Right heart pressures were obtained with a Swan-Ganz flow-directed thermodilution catheter which was also used for measuring cardiac output in conjunction with an Edwards 9500 computer, the injectate being 10 ml ice-cold 5 per cent dextrose solution. Arterial blood pressure was measured with a short polyethylene cannula inserted into the brachial artery. All pressures were recorded using Statham P23Db transducers and an Electronics for Medicine DR8 photographic recorder.

PROCEDURES

Control measurements of mean and phasic pulmonary artery, pulmonary wedge (PAWP), right atrial (RAP) and brachial artery phasic and mean pressures (MAP) were taken. Cardiac output was measured in triplicate at 2-minute intervals and results averaged. All haemodynamic measurements were repeated 30 minutes later after which one of

Table 1 *Clinical details of patients*

	Saline	*Glucose*	*Glucose-insulin-potassium*
No. of patients	13 M, 2 F	8 M, 1 F	11 M, 1 F
Age (y)	55 (range 36 to 69)	57 (range 32 to 68)	55 (range 41 to 67)
Site of infarction	11 inf., 4 ant.	5 inf., 4 ant.	7 inf., 5 ant.
Duration of symptoms to intervention	7·5 hours (range 4 to 14)	8 hours (range 5 to 14)	8 hours (range 4 to 11·5)

M, males; F, females; inf., inferior; ant., anterior.

the following infusions was given:

(a) *Glucose-insulin-potassium*
Two ml/kg 50 per cent glucose (5·55 mmol/kg) was given intravenously over 10 minutes, followed 5 minutes later by 0·4 unit/kg soluble insulin (Burroughs Wellcome). This was followed immediately by an infusion of 1·5 ml/kg per hr of 50 per cent glucose (4·2 mmol/kg per hr) to which 0·3 unit/kg soluble insulin and 0·15 mmol/kg potassium chloride were added.

(b) *50 per cent Glucose*
Two ml/kg 50 per cent glucose (5·55 mmol/kg) was given over 10 minutes followed by an infusion of 1·5 ml/kg per hr (4·2 mmol/kg per hr).

(c) *Normal saline*
Two ml/kg normal saline was given over 10 minutes, followed by an infusion of 1·5 ml/kg per hr (4·2 mmol/kg per hr).

Haemodynamic measurements were made at 30 and 60 minutes after the start of each infusion, after which the arterial cannula and the Swann-Ganz catheter were removed. To investigate the effect of the infusions on infarct size as measured by serial CK estimations, the glucose-insulin-potassium and glucose infusions were continued for 6 hours (3 patients) or 12 hours (18 patients). Saline infusion, however, was stopped after haemodynamic measurements were completed. Blood was withdrawn 2-hourly from the intravenous cannula for 6 or 12 hours (28 patients) for the estimation of serum glucose and potassium by a Technicon Autoanalyser, and 2 to 4-hourly for 36 to 72 hours in all patients for the measurement of infarct size from serial estimation of serum CK activity. In our modification (Norris *et al.*, 1975) of the method of Sobel and colleagues (Sobel *et al.*, 1972), accuracy of the calculations of total enzyme release is improved by the use of individualised figures for the degradation rate (K_D) of CK. Enzyme activity of the serial specimens was measured by the method of Rosalki (1967) using a Unicam SP-800 spectrophotometer at 340 nm, and results were expressed as the total CK release ($Et + \Sigma Edt\ K_D$) (Sobel *et al.*, 1972) in IU per ml serum. Results were not accepted unless K_D for CK could be estimated within 95 per cent confidence limits of ± 15 per cent (Norris *et al.*, 1975).

Mean arterial pressure (MAP) was obtained by electronic integration; pulmonary artery end diastolic pressure (PADP) was obtained by averaging the values of the pressures over at least one respiratory cycle.

Student's t test was used to evaluate the statistical significance of the results.

Left ventricular stroke work index (LVSWI) was calculated as follows (Crexells *et al.*, 1973):

$$\text{LVSWI} = (\text{MAP–PADP}) \times \frac{\text{Cardiac Index (ml/min per m}^2)}{\text{Heart Rate (beats/min)}} \times 0{\cdot}0144 \text{ (g m/beat per m}^2).$$

Results

MEASUREMENTS OF CARDIAC INDEX AND PULMONARY ARTERY END DIASTOLIC PRESSURE

The reproducibility of cardiac output measurements with the thermodilution technique in our laboratory, as calculated by the variation about the mean of triplicate measurements, was 5 ± 4 per cent (mean ±1SD). Pulmonary artery end diastolic pressure was used as an indirect measurement of left ventricular filling pressure, as technically satisfactory records of pulmonary artery wedge pressure were not obtained in all patients. The correlation coefficient of pulmonary artery end diastolic pressure with pulmonary wedge pressure in those patients in whom measurements of wedge pressure could be made was $r = 0{\cdot}91$ (61 comparisons in 18 patients).

CLINICAL EFFECTS

Of the 36 patients, 3 died in hospital (1 in the glucose-insulin-potassium group and 2 in the glucose group), while a fourth patient in the glucose-insulin-potassium group was successfully resuscitated from ventricular fibrillation 4 hours after entry to the trial, and while she was receiving the infusion. The patient in the glucose-insulin-potassium group who died had an anterior and inferior infarct, and developed acute right bundle-branch block 12 hours after completion of an uneventful haemodynamic study and infusion; subsequently total CK release was high at 5·2 IU/ml, indicating that he had a large infarct, and he complained of slight nocturnal breathlessness requiring treatment with a diuretic. On the thirteenth day he collapsed with ventricular fibrillation after further chest pain, and resuscitation was unsuccessful. Two patients died suddenly while still receiving glucose infusions, 6 and 9 hours after the infusions were started; in both cases necropsy showed the presence of haemopericardium. The mechanism of death in 1 patient was ventricular fibrillation, and necropsy showed occlusion of the left anterior descending artery and anterior myocardial infarction with cardiac rupture and pericardial tamponade. The second patient died in 'acute pump failure' (Lown *et al.*, 1967); necropsy showed occlusion of the left anterior descending artery, a haemorrhagic anterior infarct, and 150 ml of blood clot in the pericardium. There was no definite evidence of cardiac rupture, and the amount of blood in the pericardial cavity was insufficient to have caused tamponade. Neither of these patients had clinical evidence of cardiac failure before their death, but both had high blood sugar levels of 48·3 mmol/l and 20 mmol/l, respectively, at the time of cardiac arrest. No deaths occurred among the 15 patients who received normal saline.

The fourth patient, from the glucose-insulin-potassium group referred to above, also had an anterior infarct and was resuscitated from ventricular fibrillation 4 hours after the infusion started. The arrhythmia occurred while the infusion was still in progress, and immediately after the event, blood glucose and serum potassium were 13·1 mmol/l and 4·3 mmol/l, respectively. Because of the necessity for electrical defibrillation, figures for CK release were considered unreliable and not included in the analysis.

None of the other surviving patients had cardiac complications attributable to the infusions. In particular, no patient developed overt cardiac failure or an increase in chest pain. Most of the patients receiving the glucose and glucose-insulin-potassium infusions had a feeling of increased warmth accompanied by osmotic diuresis.

HAEMODYNAMIC CHANGES

Table 2 summarises the haemodynamic effects of saline, glucose, and glucose-insulin-potassium in 28 patients. The 2 measurements of each variable recorded at 30-minute intervals before infusion was started were not significantly different, and were averaged to provide the control data. For the three groups, the control data were found to be statistically comparable. Within each group, the duration of symptoms to intervention did not appear to affect changes in haemodynamic variables.

Saline infusion had no significant effect on the 4 haemodynamic variables which we measured, namely heart rate, mean arterial pressure, pulmonary artery end diastolic pressure, or cardiac index. In contrast, glucose infusion increased mean arterial pressure by 18 per cent ($P < 0·001$) at 30 minutes and by 14 per cent ($P < 0·005$) at 60 minutes, and increased pulmonary artery end diastolic pressure by 42 per cent ($P < 0·001$) at 30 minutes and 25 per cent ($P < 0·005$) at 60 minutes. Cardiac index also rose significantly at 60 minutes (+22%; $P < 0·05$), but heart rate did not change. Infusion of glucose-insulin-potassium resulted in significant increases in heart rate (13%; $P < 0·05$), mean arterial pressure (15%; $P < 0·01$), and pulmonary artery end diastolic pressure (27%; $P < 0·025$), at 30 but not at 60 minutes (Table 2). Cardiac index increased at 30 minutes (26%; $P < 0·005$) and at 60 minutes (22%; $P < 0·001$). The haemodynamic effects of glucose and glucose-insulin-potassium were thus similar with respect to mean arterial pressure, pulmonary artery end diastolic pressure, and cardiac index, with glucose-insulin-potassium having, in addition, a positive chronotropic response of borderline statistical significance.

Of the derived indices, systemic resistance was not affected by infusion of saline, glucose, or glucose-insulin-potassium. Left ventricular stroke work index was, however, increased significantly both by glucose and by glucose-insulin-potassium, the rise after glucose being 17 per cent ($P < 0·02$) at 30 minutes and 27 per cent ($P < 0·02$) at 60 minutes, and after glucose-insulin-potassium 25 per cent ($P < 0·02$) at 30 minutes and 22 per cent ($P < 0·005$) at 60 minutes after the start of the infusions.

Fig. 1 shows the effects of the 3 infusion regimens

Table 2 *Haemodynamic effects of normal saline, glucose, and glucose-insulin-potassium in patients with acute myocardial infarction*

Haemodynamic variables	*Saline (N = 12)*			*Glucose (N = 8)*			*Glucose-insulin-potassium (N = 10)*		
	C	*30 min*	*60 min*	*C*	*30 min*	*60 min*	*C*	*30 min*	*60 min*
HR (beat/min)	77 ±6	72 ±5 NS	74 ±4 NS	72 ±5	75 ±4 NS	74 ±4 NS	79 ±6	89 ±6 $P < 0·05$	85 ±6 NS
MAP (mmHg)	93 ±5	91 ±6 NS	93 ±6 NS	90 ±7	106 ±7 $P < 0·001$	103 ±7 $P < 0·005$	85 ±4	98 ±7 $P < 0·01$	93 ±7 NS
PADP (mmHg)	13 ±1	14 ±1·5 NS	15 ±1·5 NS	12 ±1	17 ±2 $P < 0·001$	15 ±2 $P < 0·02$	11 ±1	14 ±1·5 $P < 0·025$	12 ±2 NS
CI (l/min per m^2)	2·6 ±0·2	2·5 ±0·2 NS	2·6 ±0·2 NS	2·6 ±0·19	2·9 ±0·17 NS	3·1 ±0·28 $P < 0·05$	2·6 ±0·12	3·3 ±0·18 $P < 0·005$	3·2 ±0·16 $P < 0·001$
SRI (units per m^2)	32·7 ±2·2	33·5 ±2·6 NS	32·1 ±1·7 NS	33·8 ±5·0	35·1 ±5·0 NS	34·6 ±5·0 NS	30·9 ±1·8	28·5 ±2·7 NS	28·0 ±2·6 NS
LVSWI (g m/m^2 per beat)	39·8 ±4·7	40·3 ±5·0 NS	39·8 ±4·7 NS	43·5 ±4·1	50·9 ±3·1 $P < 0·02$	55·4 ±4·9 $P < 0·02$	36·3 ±3·7	46·2 ±5·1 $P < 0·02$	44·8 ±5·0 $P < 0·005$

All data shown are means ± SEM. N, number of patients per group.
Abbreviations: NS, not statistically significant; HR, heart rate; MAP, mean arterial pressure; PADP, pulmonary artery diastolic pressure; CI, cardiac index; SRI, systemic resistance index; LVSWI, left ventricular stroke work index.

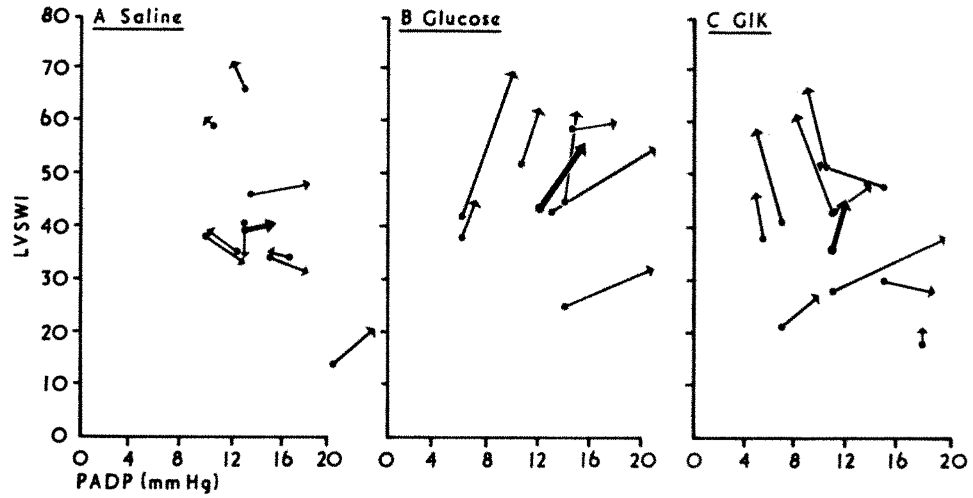

Fig. 1 *Relation between pulmonary artery end diastolic pressure (PADP) and left ventricular stroke work index (LVSWI). The dots are control values, and the arrowheads are values 60 minutes after infusion. The thick lines are the mean values for each group, while the other lines represent individual patients.*

on ventricular function as shown by plotting pulmonary artery end diastolic pressure (abscissa) against left ventricular stroke work index (ordinate) measured at 60 minutes after each intervention. It is apparent that in the case of glucose (panel B) and glucose-insulin-potassium (panel C), there were significant increases in left ventricular stroke work index associated with smaller increments in pulmonary artery end diastolic pressure. In contrast, in the saline group (panel A) only a slight increase in pulmonary artery end diastolic pressure occurred, with no effect on calculated left ventricular stroke work index.

BIOCHEMICAL CHANGES

The changes in blood glucose levels during the administration of the 3 regimens are presented in Fig. 2. The control values were similar in the 3 groups. In the saline group there was a slight and insignificant increase in the blood glucose over the next 12 hours. The blood glucose levels after glucose and glucose-insulin-potassium infusions were not significantly different, though a wide variation in levels among individual patients was noted. In these two groups, maximal levels of approximately 33·3 mmol/l were found during the first 4 hours.

Serum potassium levels (Fig. 2) were in general within normal limits during the period of infusion in the saline and glucose-insulin-potassium groups. In the glucose group, levels similar to those in the other 2 groups were found in the first 6 hours, but in the ensuing 6 hours a slight fall was noted.

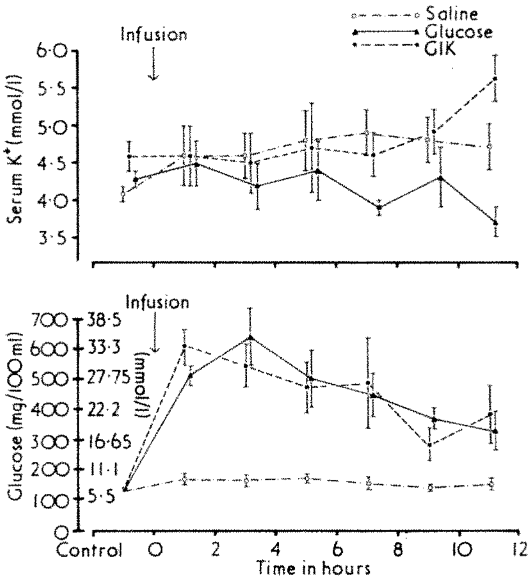

Fig. 2 *Blood glucose and serum potassium levels before and after infusion. Mean ± 1 SEM for each group at 2-hourly intervals. Control blood glucose levels in the 3 groups were similar.*

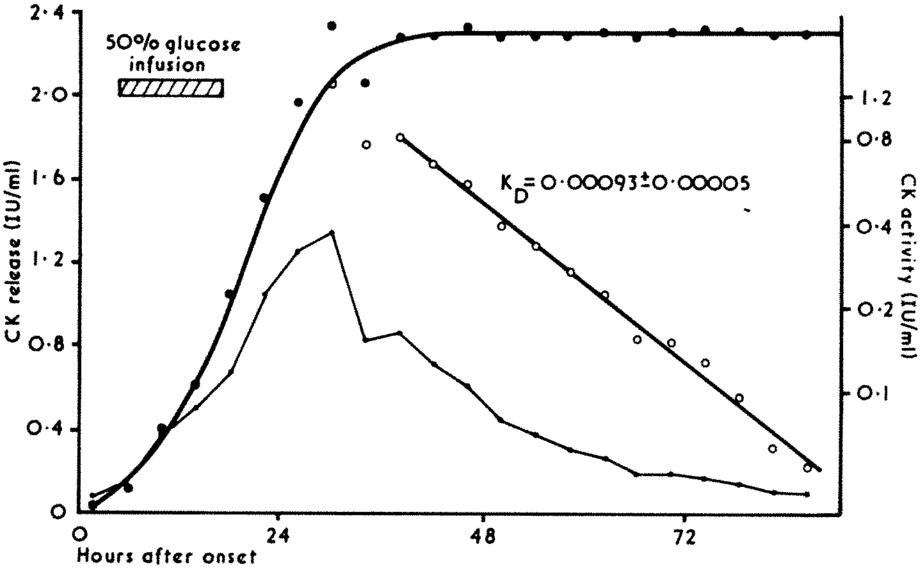

Fig. 3 *Serum CK activity measurements in a patient who had infusion of 50 per cent glucose. Serial serum CK activity levels (small closed circles), and a semilogarithmic replot of the same levels from the peak of activity downwards (open circles) are shown, together with the calculated integrated appearance function* ($Et + K_D\Sigma Edt$, *large closed circles) for each measurement. An assumed normal value of 0·04 IU/ml (40 mIU/ml) has been subtracted from all measurements. The degradation rate* (K_D) *was calculated from 13 points on the descending level of CK activity. In some cases (not in this example) the early part of the down-slope is omitted for the calculation of* K_D *because a slower rate of decline, as determined by visual inspection, might signify continuing release of CK from the infarct despite falling serum levels. Similarly in other examples the last part of the downslope (below about 200 mIU/ml) is omitted because error caused by uncertainty about the precise normal level of CK activity for the patient under consideration increases as the activity approaches normal. The integrated appearance function (total CK release as calculated from the 4-hourly serum levels and the observed* K_D) *is approximately 2·3 IU/ml in this patient, and enzyme release is complete at 35 to 40 hours after the onset of chest pain. The slope of the integral curve before this time is proportional to the velocity of enzyme release.*

CREATINE KINASE RELEASE

Total CK release as measured by integral ($ET + \Sigma Edt\ K_D$) (Sobel *et al.*, 1972; Norris *et al.*, 1975) was determined in 30 of the 36 patients. The method used for calculation of the integral is summarised in Fig. 3. Reasons for failure to record the integral were early death before K_D enzyme degradation could be measured (2 cases), the necessity for electrical defibrillation (1 case), unacceptably wide 95 per cent confidence limits for K_D (Norris *et al.*, 1975) (2 cases), and technical difficulties with venesection (1 case). The degradation rate (K_D) for CK was not affected by glucose or glucose-insulin-potassium. The mean K_D for patients given saline was 0·00103 ± 0·0039 (SD) min^{-1}, while for patients given glucose it was 0·00097 ± 0·00020 min^{-1}, and for patients given glucose-insulin potassium, 0·00106 ± 0·00020 min^{-1}.

Figures for total CK release are shown in Fig. 4; as we have previously noted (Norris *et al.*, 1975), a wide scatter of values occurs, so that no significant differences were apparent among the 3 treatment groups. In addition, the duration of symptoms before intervention did not appear to bear on the value for total CK release within each group; we have also noted previously that calculation of the integral is not affected if the start of sampling is delayed for up to 12 hours after the onset of infarction.

There was a tendency for patients with inferior infarction treated with glucose or glucose-insulin-potassium to have larger infarcts (assessed by CK integral) than those treated with normal saline. The mean integral for patients treated with glucose-insulin-potassium or glucose was 2·1 IU/ml (SEM 0·4, n = 10), while for those treated with normal saline it was 1·3 IU/ml (SEM 0·3, n = 10). The difference between the two groups was not significant (unpaired t test; t = 1·49; $0{\cdot}1 < P < 0{\cdot}2$). It was interesting to examine the curves of total CK release in order to determine whether the tendency towards higher enzyme release among treated patients could be accounted for by a 'washout' of enzyme activity resulting from improved perfusion of ischaemic myocardium (Roe and Starmer, 1975). This postulated mechanism could lead to a paradoxical increase in enzyme release without a concomitant increase in infarct size. However, when the proportion of total enzyme release which occurred during 12 hours after the start of therapeutic intervention was compared with that over a similar period in patients receiving normal saline, no difference was apparent.

An insufficient number of cases of anterior infarction was available for statistical analysis of enzyme release, the result in part of the fact that 3 of the 4 patients with anterior infarction who had cardiac arrest did so before total CK release could be determined; all of these patients were receiving glucose or glucose-insulin-potassium. Because of the apparently detrimental effect of glucose and glucose-insulin-potassium on the clinical status and the extent of enzyme release in these initial studies, detailed observations in larger numbers of patients were considered ethically unjustifiable.

Discussion

Our study has clearly shown that after acute myocardial infarction in man, glucose and glucose-insulin-potassium improve left ventricular function as judged by increases in left ventricular stroke work index and cardiac index. These results are consistent with a positive inotropic action as has also been reported in patients with ischaemic heart failure and in experimental animals with anoxic myocardium (Sodi-Pollares *et al.*, 1966). The mechanism of the inotropic effect of glucose and glucose-insulin-potassium is not, however, fully understood.

It has been postulated that augmentation of glucose supply to the heart enhances anaerobic glycolysis (Maroko *et al.*, 1972; Majid *et al.*, 1972; Austen *et al.*, 1965), as indicated by studies which have shown increased myocardial glucose uptake after experimental coronary occlusion in dogs (Owen *et al.*, 1969; Brachfeld and Scheuer, 1967). Such an action should produce an early change in cardiac function from the sudden increase in fuel supply to the ischaemic myocardium, and was the rationale for the timing of the haemodynamic measurements in the present study. Alternatively, improvement in myocardial function might result from a reduction in infarct size (Maroko *et al.*, 1972). A change in cardiac function resulting from actual anatomical improvement, however, could appear late and might not be shown by our haemodynamic procedure.

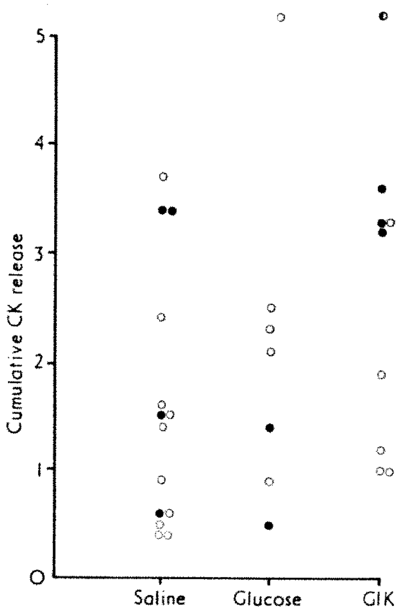

Fig. 4 *Total creatine kinase* (CK) release (IU/ml) in 30 patients receiving either saline, glucose, or glucose-insulin-potassium (GIK). Closed circles denote patients with anterior infarction; open circles, patients with inferior infarction; and the composite closed and open circle a patient with combined anterior and inferior infarction.*

If the improvement in haemodynamics found in our study was the result of enhanced glucose utilisation, the fact that glucose-insulin-potassium and glucose infusions produced similar effects is of interest. It suggests either that the dose of insulin in our glucose-insulin-potassium infusion (based on Maroko *et al.*, 1972) was inadequate, or that sufficient endogenous insulin was available in the patients given glucose alone to allow glucose uptake comparable with that in the glucose-insulin-potassium group, despite reports that intrinsic insulin secretion is suppressed after myocardial infarction in man (Allison *et al.*, 1969; Taylor *et al.*, 1969). Serum insulin levels were not measured in our patients since our main objectives were to investigate the effects of glucose infusions, with and without insulin, on infarct size and myocardial function after acute myocardial infarction. The finding of Lesch and colleagues (1974), however, suggests that serum insulin levels in our patients treated with glucose-insulin-potassium were substantially increased. Despite using a smaller dose of insulin than that employed in the present study, Lesch found that immunoreactive insulin in his subjects was increased 20 to 100 fold. Alternatively, it is also possible that in the presence of high glucose levels, as found in the present study, increased myocardial glycolysis could occur without insulin (Morgan *et al.*, 1961; Weissler *et al.*, 1968).

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* The method used for the calculation of total CK release is summarised in Fig. 3.

A further quite different possibility is that the stimulatory haemodynamic effects of glucose and glucose-insulin-potassium were unrelated to any myocardial metabolic effects, but were caused by an increase in blood volume after infusion of the hypertonic solutions. Though plasma volumes were not measured, this appears likely as the increase in left ventricular stroke work index which occurred in our patients was associated with a concomitant increase in left ventricular preload measured indirectly by the pulmonary artery end diastolic pressure, indicating that the inotropic effect was the result in part of the Frank-Starling mechanism. This could have resulted from diastolic stretching of the ventricles because of an increase in plasma volume after infusion of the hypertonic solutions. Hyperosmolar infusions are believed to have other salutary effects on the ischaemic myocardium in reducing cellular oedema and improving tissue perfusion (Leaf, 1973). The change in blood glucose levels suggests that osmolality must have increased by over 20 mosm/kg H_2O after intervention with glucose and glucose-insulin-potassium. Experimental and clinical studies have shown that an increase in osmolality of this order produces significant improvement in myocardial contractile function (Wildenthal *et al.*, 1969; Willerson *et al.*, 1973). Furthermore, hyperosmolar infusions have also been shown to cause sympathetically-mediated increases in heart rate and arterial pressure (Holland *et al.*, 1959; Lasser *et al.*, 1960), which were found in our subjects.

The failure of other workers (Most *et al.*, 1972; Lesch *et al.*, 1974) to show a stoichiometric relation between myocardial glucose uptake and lactate release during glucose-insulin-potassium infusion in man also argues against glucose-insulin-potassium and glucose having any stimulant effect on anaerobic glycolysis. The absence of such a relation has recently been confirmed in our own experimental laboratory, since we failed to show increased glucose uptake after glucose-insulin-potassium in the acutely ischaemic myocardium after ligation of the left anterior descending coronary artery in dogs (Heng *et al.*, 1976). Moreover, studies by Rovetto and colleagues (Rovetto *et al.*, 1973) in the ischaemic rat heart have shown that, during ischaemia, glycolytic flux is reduced and cannot be stimulated by glucose or glucose-insulin-potassium. This was attributed to an increase in intracellular acidity resulting from the accumulation of lactate in the poorly perfused ischaemic myocardium.

Although the present study was prompted by reports that glucose-insulin-potassium and glucose have a protective effect on the myocardium in experimental infarction (Maroko *et al.*, 1972), our results indicate that intervention with these regimens in man may enhance myocardial oxygen demand by producing increases in left ventricular stroke work index, heart rate, and mean aortic pressure (Sarnoff and Braunwald, 1962). These changes, however, may not be necessarily detrimental, as the ultimate effect on infarct size will depend on the balance between the increase in myocardial oxygen demand and that of improved coronary perfusion resulting from increased arterial pressure (Maroko *et al.*, 1971). It was hoped that definitive answers to these questions could be provided by the estimation of infarct size as measured by enzyme release. These measurements did not reveal a favourable trend in the alteration of infarct size; indeed there was a tendency in patients with inferior infarcts for total CK release to be greater among patients given glucose or glucose-insulin-potassium than among those given saline. This tendency, however, did not reach statistical significance because of the wide range of enzyme release which occurred. Though we tried to select a homogeneous group of patients on clinical criteria, the size of infarcts varied up to tenfold, and the range from 4 to 14 hours from the time of onset to intervention added a further variable. Thus, in order to show a difference in infarct size between two groups of patients, the number studied would have to be large, and it might be necessary for intervention to be made within a shorter period such as 4 to 6 hours after the onset. We considered it ethically unjustifiable to expand the present study further, however, as we were concerned not only with the apparently unfavourable trends with enzyme release after glucose and glucose-insulin-potassium infusions, but also with the fact that 3 treated patients had cardiac arrests during infusion, compared with no complications in the control group. Though the number of patients required to permit statistically significant conclusions may be much less with the curve-fitting procedure suggested by Shell and colleagues (Shell *et al.*, 1973), the necessity to withhold therapeutic intervention for several hours after admission is a serious objection to this technique.

Our findings of a negative and possibly deleterious effect of glucose and glucose-insulin-potassium are in agreement with those of Reduto *et al.* (1974) who infused a smaller dose of glucose-insulin-potassium later after the onset of infarction than was the case in our study. They may also be complementary to those of Lesch *et al.* (1974) who noted signs of enhanced ischaemia after glucose-insulin-potassium in 5 of 8 patients with angina pectoris subjected to atrial pacing stress. Our data and those of Lesch *et al.* (1974) do not nevertheless exclude the possibility that glucose and glucose-insulin-potassium administration in cardiogenic shock may be beneficial.

References

Allison, S. P., Chamberlain, M. J., and Hinton, P. (1969). Intravenous glucose tolerance, insulin, glucose, and free fatty acid levels after myocardial infarction. *British Medical Journal*, **4,** 776–778.

Austen, W. G., Greenberg, J. J., and Piccinini, J. C. (1965). Myocardial function and contractile force affected by glucose loading of the heart during anoxia. *Surgery*, **57,** 839–845.

Ballard, F. B., Danforth, W. H., Naegle, S., and Bing, R. J. (1960). Myocardial metabolism of fatty acids. *Journal of Clinical Investigation*, **39,** 717–723.

Brachfeld, N. (1973). The glucose-insulin-potassium (GIK) regimen in the treatment of myocardial ischaemia. *Circulation*, **48,** 459–462.

Brachfeld, N., and Scheuer, J. (1967). Metabolism of glucose by the ischaemic dog heart. *American Journal of Physiology*, **212,** 603–606.

Crexells, C., Chatterjee, K., Forrester, J. S., Dikshit, K., and Swan, H. J. C. (1973). Optimal level of filling pressure in the left side of the heart in acute myocardial infarction. *New England Journal of Medicine*, **289,** 1263–1266.

De Leiris, J., Opie, L. H., and Lubbe, W. F. (1975). Effects of free fatty acid and glucose on enzyme release in experimental myocardial infarction. *Nature*, **253,** 746–747.

Evans, J. R. (1964). Importance of fatty acid in myocardial metabolism. *Circulation Research*, **15,** Suppl. II, 96–106.

Heng, M. K., Singh, B. N., Peter, T., Nisbet, H. D., and Norris, R. M. (1976). The effects of glucose-insulin-potassium in experimental myocardial infarction in the dog. Submitted for publication.

Holland, R. C., Sundsten, J. W., and Sawyer, C. H. (1959). Effects of intracarotid injections of hypertonic solutions on arterial pressure in the rabbit. *Circulation Research*, **7,** 712–720.

Lasser, R. P., Schoenfeld, M. R., Allen, D. F., and Friedberg, C. K. (1960). Reflex circulatory effects elicited by hypertonic and hypotonic solutions injected into femoral and brachial arteries of dogs. *Circulation Reseach*, **8,** 913–919.

Leaf, A. (1973). Cell swelling. A factor in ischemic tissue injury. *Circulation*, **48,** 455–458.

Lesch, M., Teichholz, L. E., Soeldner, J. S., and Gorlin, R. (1974). Ineffectiveness of glucose, potassium and insulin infusion during pacing stress in chronic ischaemic heart disease. *Circulation*, **49,** 1028–1037.

Lown, B., Fakhro, A. M., Hood, W. B., and Thorn, G. W. (1967). The coronary-care unit. *Journal of the American Medical Association*, **199,** 188–198.

Majid, P. A., Sharma, B., Meeran, M. K. M., and Taylor, S. H. (1972). Insulin and glucose in the treatment of heart failure. *Lancet*, **2,** 937–941.

Maroko, P. R., Kjekshus, J. K., Sobel, B. E., Watanabe, T., Covell, J. W., Ross, J., and Braunwald, E. (1971). Factors influencing infarct size following experimental coronary artery occlusions. *Circulation*, **43,** 67–82.

Maroko, P. R., Libby, P., Sobel, B. E., Bloor, C. M., Sybers, H. D., Shell, W. E., Covell, J. W., and Braunwald, E. (1972). Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. *Circulation*, **45,** 1160–1175.

Medical Research Council Working Party on the Treatment of Myocardial Infarction (1968). Potassium, glucose and insulin treatment for acute myocardial infarction. *Lancet*, **2,** 1355–1360.

Mittra, B. (1965). Potassium, glucose, insulin in treatment of myocardial infarction. *Lancet*, **2,** 607–609.

Morgan, H. E., Henderson, M. J., Regan, D. M., and Park, C. R. (1961). Regulation of glucose uptake in muscle. I. The effects of insulin and anoxia on glucose transport and phosphorylation in the isolated, perfused heart of normal rats. *Journal of Biological Chemistry*, **236,** 253–261.

Most, A. S., Gorlin, R., and Soeldner, J. S. (1972). Glucose extraction by the human myocardium during pacing stress. *Circulation*, **45,** 92–96.

Norris, R. M., Whitlock, R. M. L., Barratt-Boyes, C., and Small, C. W. (1975). Clinical measurement of myocardial infarct size. Modification of a method for the estimation of total creatine phosphokinase release after myocardial infarction. *Circulation*, **51,** 614–620.

Owen, P., Thomas, M., and Opie, L. (1969). Relative changes in free-fatty-acid and glucose utilisation by ischaemic myocardium after coronary artery occlusion. *Lancet*, **1,** 1187–1190.

Reduto, L., Gulotta, S., and Morrison, J. (1974). Ineffectiveness of glucose-insulin-potassium infusion on ischemic myocardium. *Clinical Research*, **22,** 685A.

Roe, C. R., and Starmer, C. F. (1975). A sensitivity analysis of enzymatic estimation of infarct size. *Circulation*, **52,** 1–5.

Rosalki, S. B. (1967). An improved procedure for serum creatine phosphokinase determination. *Journal of Laboratory and Clinical Medicine*, **69,** 696–705.

Rovetto, M. J., Whitmer, J. T., and Neely, J. R. (1973). Comparison of the effects of anoxia and whole heart ischemia on carbohydrate utilization in isolated working rat hearts. *Circulation Research*, **32,** 699–711.

Sarnoff, S. J., and Braunwald, E. (1962). Hemodynamic determinants of myocardial oxygen consumption. In *Cardiovascular Functions*, p. 24. Ed. by A. A. Luisada. McGraw-Hill, New York.

Shell, W. E., Lavelle, J. F., Covell, J. W., and Sobel, B. E. (1973). Early estimation of myocardial damage in conscious dogs and patients with evolving acute myocardial infarction. *Journal of Clinical Investigation*, **52,** 2579–2590.

Sobel, B. E., Bresnahan, G. F., Shell, W. E., and Yoder, R. D. (1972). Estimation of infarct size in man and its relation to prognosis. *Circulation*, **46,** 640–648.

Sodi-Pallares, D., Bisteni, A., Medrano, G. A., De Micheli, A., Ponce de León, J., Calva, E., Fishleder, B. L., Testelli, M. R., and Miller, B. L. (1966). The polarising treatment in cardiovascular conditions. Experimental basis and clinical applications. In *Electrolytes and Cardiovascular Diseases*, p. 198. Ed. by E. Bajusz. S. Karger, A.G., Basel.

Taylor, S. H., Saxton, C., Majid, P. A., Dykes, J. R. W., Ghosh, P., and Stoker, J. B. (1969). Insulin secretion following myocardial infarction with particular respect to the pathogenesis of cardiogenic shock. *Lancet*, **2,** 1373–1378.

Weissler, A. M., Kruger, F. A., Baba, N., Scarpelli, D. G., Leighton, R. F., Gallimore, J. K. (1968). Role of anaerobic metabolism in the preservation of functional capacity and structure of anoxic myocardium. *Journal of Clinical Investigation*, **47,** 403–416.

Wildenthal, K., Mierzwiak, D. S., and Mitchell, J. H. (1969).

Acute effects of increased serum osmolality on left ventricular performance. *American Journal of Physiology*, **216**, 898–904.

Willerson, J. T., Curry, G. C., Atkins, J. M., Wildenthal, K., and Horwitz, L. D. (1973). The influence of hypertonic mannitol on hemodynamics and coronary blood flow in patients. *Circulation*, **47-48**, Suppl. IV–7.

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Early work load tests for evaluation of long-term prognosis of acute myocardial infarction

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Exercise tests performed 3 and 9 weeks after acute myocardial infarction in 205 patients were found to give prognostic information on the survival during a follow-up period of 2 to 5 years. The appearance of tachycardia, major ventricular arrhythmias, or anginal complaints during these early exercise tests was thus accompanied by a significantly increased mortality during the observation period. Ventricular arrhythmias disclosed by exercise proved to be of higher prognostic significance than those recorded at rest on the same occasions. The usefulness of early exercise tests in the evaluation of the response to antiarrhythmic treatment after acute myocardial infarction as well as of the prognostic importance of the effects was documented in a smaller series of patients.

Modern coronary care units (CCU) have led to an appreciable reduction of the early mortality in acute myocardial infarction. This improvement is probably mainly the result of the early detection and treatment of arrhythmias. The mortality during the first years after an acute myocardial infarction, however, remains high and has been found to be correlated with ventricular arrhythmias observed on the resting electrocardiogram recorded at discharge from hospital (Lown and Wolf, 1971; Helmers, 1973; Coronary Drug Project Research Group, 1973). In a previous investigation (Ericsson *et al.*, 1973), we have drawn attention to the value of an early post-acute myocardial infarction exercise test to disclose limiting factors and arrhythmias. The present investigation, which is an extended retrospective study, aims at evaluating the results from these early exercise tests in relation to the long-term prognosis as well as the potential value of these tests in the therapeutic management of the patients, with special reference to arrhythmias.

Subjects

Studies were made on 205 patients in whom it had been possible to perform an early exercise test after an acute myocardial infarction. There were 183 men and 22 women with a mean age of 59 ±9 years (mean ± 1 SD) for the entire group.

In accordance with our previous study (Ericsson *et al.*, 1973) a diagnosis of acute myocardial infarction was based on the fulfilment of at least two of the following criteria:

(1) Acute central chest pain lasting for at least 30 minutes.

(2) Rise in aspartate aminotransferase (SGOT), with values higher than those for alanine aminotransferase, or lactic dehydrogenase iso-enzyme, which in a few cases was diagnostic when only moderate rises in aspartate aminotransferase were seen.

(3) Electrocardiographic pattern compatible with acute myocardial infarction. In the diagnosis of true posterior infarcts a vector-electrocardiogram (Frank-system) was used.

The location of the infarction was anteroseptal or anterolateral in 99 cases, inferior in 57, and posterior in 10 cases. In 32 cases multiple infarcts were diagnosed whereas in 7 patients no exact location could be obtained.

The present infarction was considered to be the first acute myocardial infarct in 168 of the patients. Thirty patients had had one acute myocardial infarct previously and 7 patients had had two or more infarcts.

The patients were treated in the CCU at Danderyd Hospital during the period April 1970 to March 1973, during which time 430 patients were treated for acute myocardial infarction (Fig. 1). The hospital mortality was 20 per cent (84 patients). There were 172 patients aged more than 65 years

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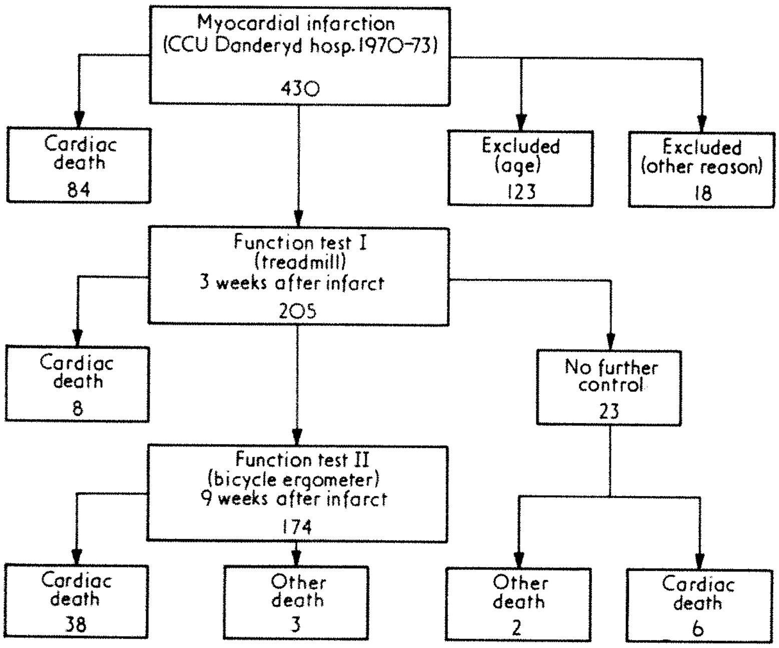
Myocardial infarction (CCU Danderyd hosp. 1970-73) 430
Cardiac death 84
Excluded (age) 123
Excluded (other reason) 18
Function test I (treadmill) 3 weeks after infarct 205
Cardiac death 8
No further control 23
Function test II (bicycle ergometer) 9 weeks after infarct 174
Cardiac death 38
Other death 3
Other death 2
Cardiac death 6

Fig. 1 *Patient group subjected to exercise testing 3 and 9 weeks, respectively, after an acute myocardial infarct and groups of patients excluded and deceased.*

and in 123 of these cases no early work-load test was performed mainly because of lack of resources in the laboratory at the start of the study and in some cases because of general disability. A further 18 patients were excluded from the early exercise test because of transfer to other departments (12) or other complicating disease (6).

On the remaining 205 patients a treadmill test was performed 3 weeks after the onset of the acute illness after a period of increasing mobilisation under the guidance of a physiotherapist. In 174 patients a further outpatient exercise test on a bicycle ergometer was performed 9 weeks after the acute myocardial infarction. Eight patients died before this second test and another 23 patients could not be re-evaluated for other reasons (reinfarction 9, severe heart failure 3, severe angina pectoris 1, bronchial asthma 2, acute gall-bladder disease 1, acute infection 1, general weakness 1, unknown reasons 3, and 2 patients had moved). In this group of 23 patients who could not be re-evaluated, 8 died of whom 6 were in acute cardiac disease. This mortality corresponds to that of the remaining patients who were available for re-evaluation. At follow-up of the entire patient group in March 1975, 2 to 5 years after the acute myocardial infarction, 52 of the 205 patients (25%) had died of their cardiac illness (Fig. 2). The two-year total mortality amounted to 24 per cent.

Methods

TREADMILL TEST

The first exercise test 3 weeks after the acute myocardial infarct was performed on a treadmill (Collins, P 2000). This particular type of exercise

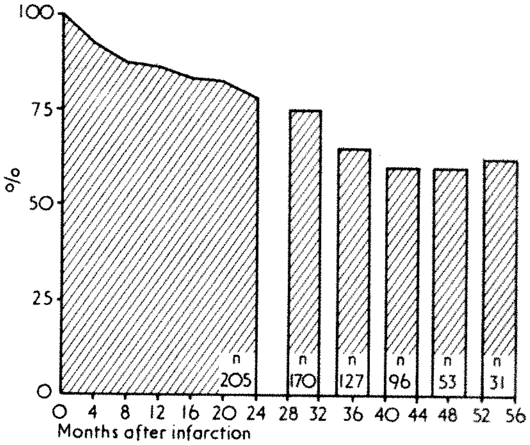

Fig. 2 *Percentage survival at various time intervals after discharge from coronary care unit (CCU) in 205 patients taking part in first exercise test. n, number of patients followed to different time intervals.*

was considered most suitable in testing the patient's ability to return to the activities of daily life. The procedure has been thoroughly described in a previous paper (Ericsson *et al.*, 1973). The walking speed was accordingly standardised to 0·5 m/s and the inclination angle adjusted to the body-weight so as to obtain an initial load of 100 or 200 kpm/min corresponding to 16 or 33 W, respectively. If possible, the load was later increased by another 16 or 33 W every 6 minutes through a further increase of the inclination angle. The treadmill test was continuously supervised by a physician and was interrupted at the appearance of anginal pain (42 patients), dyspnoea (10 patients), or alarming electrocardiographic abnormalities, notably ventricular arrhythmias (29 patients). In 7 patients exercise was interrupted because of general fatigue and in another 16 patients when the heart rate reached 140 beats/min. In the remaining 101 patients caution was the main reason for ending the exercise test with particular regard to earlier arrhythmias or the general condition of the patient.

BICYCLE TEST

The second exercise test 9 weeks after infarction was performed on an electrically braked bicycle ergometer according to the routine procedure of exercise testing at the hospital. The initial load was 33 W for 6 minutes with a stepwise increase of 33 W every 6 minutes until the test was interrupted for the same reason as the treadmill walking, i.e. anginal pain (36), dyspnoea (7), electrocardiographic abnormalities (32), fatigue (6), heart rate >140 beats/min (38), and caution (55 patients).

ELECTROCARDIOGRAM RECORDING

The electrocardiogram was recorded during supine rest for 2 minutes before each function test with a further recording during 8 minutes in a standing position before the second function test on the bicycle ergometer. During exercise the electrocardiogram was registered continuously as well as during the 10 minutes rest after break. The recordings of the resting electrocardiogram comprised conventional extremity leads and 6 praecordial leads with the reference electrode on the right arm (CR leads). During exercise the reference electrode was positioned on the forehead (CH leads). A direct writing ink-jet recorder (Mingograph 81, Siemens-Elema) was used.

Table *Some clinical data from period in coronary care unit and number of infarctions correlated to follow-up mortality*

	Dead at follow-up	*Alive at follow-up*
Age at infarction (y)	60 ±9	59 ±9
Serum aspartate aminotransferase (max), (μkatal)	3·5 ±2·6	2·9 ±2·3
Heart volume (ml per m^2)	567 ±103	483 ±136
First infarction (no. of patients)	40	128
Reinfarction (no. of patients)	17	20

Results

The mortality during the follow-up time of 2 to 5 years has been correlated with certain clinical data from the acute illness and ventricular arrhythmias observed during the stay in the coronary care unit, as well as those seen during the exercise test 3 and 9 weeks after the acute myocardial infarction (Fig. 3). The ventricular arrhythmias were defined as multifocal, paired and/or ≥ 5 ventricular ectopic beats (VEB)/min. We have also examined exercise-induced tachycardia, angina pectoris, and dyspnoea in relation to prognosis (Fig. 4).

CLINICAL DATA (Table)

When comparing the 57 patients who died during the observation time with the 142 survivors, there were no differences regarding age, cardiac size, and maximum enzyme levels (aspartate aminotransferase) as observed in the coronary care unit. In contrast, there were more deaths among those patients who had had a previous infarction as compared with those with a first infarction (17/37 and 40/168, respectively); this difference is probably significant ($P < 0{\cdot}05$).

VENTRICULAR ARRHYTHMIAS (Fig. 3)

Coronary care unit stay

During the coronary care unit stay 109 of 197 continuously monitored patients (59%) had ventricular arrhythmias. Of these 109 patients, 23 (21%) also had ventricular arrhythmias during the treadmill test 3 weeks after the acute event as compared with 10/88 (11%) of those without ventricular arrhythmia in the coronary care unit ($P < 0{\cdot}05$). In these two groups with arrhythmias at the time of the first exercise test 10 and 2 patients, respectively, were on antiarrhythmic therapy.

Resting electrocardiogram

Six patients (3%) had ventricular arrhythmias at the time of the routine resting electrocardiogram 3 weeks after the acute myocardial infarction. During the observation time one of these patients died as compared with 56/199 without ventricular arrhythmias on this recording (n.s.). Nineteen patients (11%) showed ventricular arrhythmias on

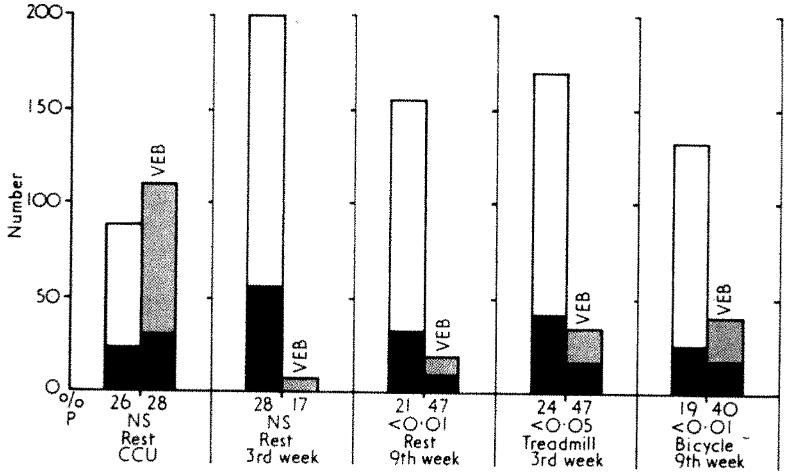

Fig. 3 *Mortality in patients with and without ventricular ectopic beats (VEB) during CCU care or at follow-up control 3 and 9 weeks after acute myocardial infarct. The solid black parts of the total bars represent number of patients dying during follow-up period within respective patient groups, with the mortality percentage presented below. P values indicate significance levels for differences in mortality as calculated from* χ^2 *analyses.*

the resting electrocardiogram taken at the time of the second exercise test 9 *weeks* after the acute myocardial infarction. Nine of these patients died during the follow-up time in comparison with 32/155 of the patients without ventricular arrhythmias, giving a significantly lower mortality in the latter group ($P < 0{\cdot}01$).

Exercise electrocardiogram

At the treadmill test 3 weeks after the acute myocardial infarction, ventricular arrhythmia was seen in 34 patients (17%). Fourteen of these were on antiarrhythmic therapy as compared with 41 of 171 patients without ventricular arrhythmias. Furthermore, 135 patients were treated for heart failure with digitalis and diuretics. The mortality for patients with ventricular arrhythmia was 16/34 in comparison with 41/171 of those without ventricular arrhythmias at this initial exercise test. The difference is probably significant ($P < 0{\cdot}05$).

Antiarrhythmic therapy was introduced in 12 of 17 patients with ventricular arrhythmias at the time of the first exercise test and altered in another 5 patients. Thirteen of these patients were given procainamide 0·5 g 4 times daily. On a repeated exercise test ventricular arrhythmias persisted in spite of altered therapy in 5 patients. Four of these 5 patients subsequently died as compared with 2 of 12 who became free from ventricular arrhythmias.

Ventricular arrhythmias were seen during the exercise test 9 weeks after the acute myocardial infarct in 40 of the 174 (23%) patients. During the

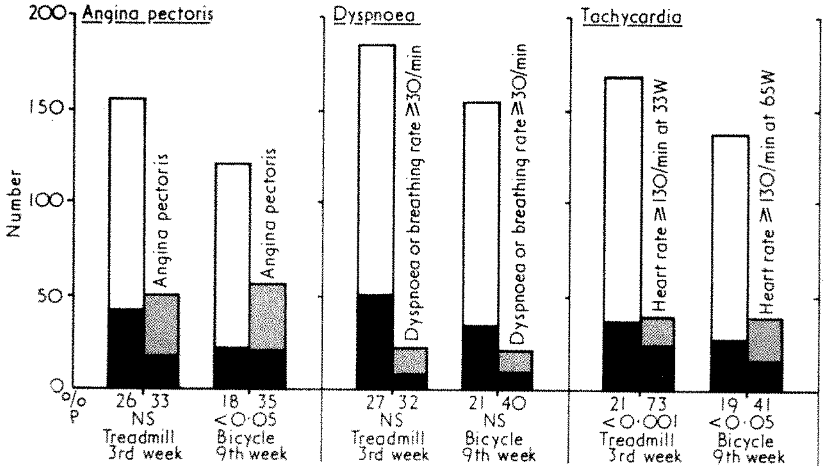

Fig. 4 *Mortality in patients with and without angina pectoris, dyspnoea, and tachycardia, respectively, in association with exercise test 3 and 9 weeks after acute myocardial infarction. Symbols as in Fig. 3.*

follow-up time 16 of these died as compared with 25 of 134 without arrhythmias, which implies a significantly higher mortality in those with ventricular arrhythmias at this stage ($P < 0{\cdot}01$).

TACHYCARDIA (Fig. 4)
At the exercise test 3 weeks after the acute myocardial infarct tachycardia, defined as heart rate ≥130/min at a workload of 33 W, was seen in 30 patients. Twenty-two of these died during the follow-up period as compared with 35 of 167 without this increase in heart rate. This difference is highly significant ($P < 0{\cdot}001$).

At the exercise test 9 weeks after the acute myocardial infarct 37 patients had a corresponding tachycardia at a load of 65 W. In this group 15 patients subsequently died as compared with 26 of 137 of the remaining patients ($P < 0{\cdot}05$).

Maximum heart rates were on an average higher at the second exercise test as compared with the first, 126 ± 18 (mean ± SD) and 117 ± 15 beats/min, respectively. The mean values for the corresponding final loads were 78 ± 24 W and 45 ± 19 W, respectively.

ANGINA PECTORIS (Fig. 4)
Angina pectoris occurring at the time of the first exercise test 3 weeks after the acute myocardial infarct did not imply a raised mortality during the follow-up time. At this test 49 patients developed angina and 16 died as compared with 41 of 156 without angina. In contrast a certain increase in mortality was seen among those patients who developed angina pectoris at the second exercise test 9 weeks after the acute myocardial infarct. Thus 19 of 55 patients with angina pectoris at this test died in comparison to 22 of 119 without.

DYSPNOEA (Fig. 4)
Dyspnoea, defined as difficulty in breathing and/or a respiratory rate ≥30/min, was seen in 22 patients during the treadmill test and 20 patients during the second exercise test on the bicycle ergometer. There was no increase in mortality in either group with dyspnoea during the follow-up.

COMPLICATIONS
One patient developed prolonged ventricular tachycardia after the bicycle ergometer test and was successfully electroconverted. No other major arrhythmias or complications occurred during these tests.

Discussion

A certain selection of patients has been made in the present study (Fig. 1), but the results obtained seem to agree well with previous studies as regards survival after acute myocardial infarction (e.g. Shanoff *et al.*, 1966; Helmers, 1973). The relative merits of long-term recording and exercise tests in the detection of severe cardiac arrhythmias after acute myocardial infarction have been discussed by several authors (Kosowsky *et al.*, 1971; Crawford *et al.*, 1974; Kentala *et al.*, 1975; Rehnqvist, 1976; Ryan *et al.*, 1975). The information obtained from prolonged supervision and exercise tests, respectively, is clearly in part dependent on the duration of the registration and the design of the exercise test. Thus Kosowsky *et al.* (1971) suggested that one is more likely to detect ventricular arrhythmias during a short exercise test as compared with a monitoring period of 2 hours. In contrast, Ryan *et al.* (1975) found that a 24-hour ambulatory recording period indicated twice as many instances of coupled ventricular ectopic beats and periods of ventricular tachycardia as exercise testing in patients with coronary artery disease. The same authors, however, suggest that these different methods probably disclose types of arrhythmias which differ in respect of both aetiology and prognostic significance. Crawford *et al.* (1974) found that a 10-hour continuous recording showed more serious arrhythmias than a treadmill exercise test but they still consider that there is a need for an evaluation of the prognostic value of exercise tests. In our opinion, exercise tests carry the advantage of standardised conditions of investigation as well as supervision of the patient. It has moreover been suggested by Ryan *et al.* (1975) that those arrhythmias which are frequent during long-term monitoring also appear during exercise testing.

In accordance with our previous investigation (Ericsson *et al.*, 1973) we again found in this extended study that the occurrence of ventricular arrhythmias during the stay in coronary care unit did not affect the long-term prognosis. On the other hand, confirmation was obtained that the occurrence of ventricular arrhythmias seen during early exercise testing was associated with a significantly raised incidence of sudden death during the years after an acute myocardial infarct. This observation is in contrast to the results recently reported by Kentala *et al.* (1975)—who by stepwise multiple discriminant analysis found the prognostic significance of ventricular arrhythmias during early exercise tests to be poor. The importance of ventricular arrhythmias as an independent risk factor after acute myocardial infarction has been stressed by Kotler *et al.* (1973) who based their conclusions on intermittent long-term recording during ordinary daily activities. Our patient group is too limited in number to allow for a closer analysis of the prognostic importance of different forms of ventricular arrhythmias. Kotler *et al.* (1973) have, however, observed that ventricular parasystole after acute myocardial infarction does not carry a worsened prognosis as regards sudden death. No major investigations of the value of antiarrhythmic therapy in patients surviving an acute myocardial infarct with persistent ventricular irritability exist today. Ryan *et al.* (1975) have pointed to the difficulties in the medical management of these arrhythmias. Kotler *et al.* (1973) also question the possibilities of preventing sudden deaths during the first years after acute myocardial infarct. In this limited patient material where it was possible to observe the antiarrhythmic effect by repeated exercise testing, a lower mortality was found among patients who became free from arrhythmias than those who remained arrhythmic (2/12 compared to 4/5). Whether this finding is a result of therapy or whether it merely reflects that a severely damaged myocardium fails to respond to therapy, cannot be answered without more extensive studies.

Our present results also show that a pronounced increase in heart rates during early exercise tests after acute myocardial infarct carries a poor prognosis. It is probable that these raised heart rates reflect a poor stroke volume caused by impaired myocardial function. Similarly, decreased myocardial function after an acute myocardial infarct probably also accounts for the unfavourable prognosis associated with a poor systolic pressure rise during exercise in these patients (Kentala *et al.*, 1975). Tachycardia might sometimes merely have been an expression of a raised sympathetic drive, factor which, however, also may affect the prognosis.

Our observation of a worsened prognosis associated with angina pectoris developing during early exercise tests after an acute myocardial infarct suggests that the degree of coronary insufficiency has its obvious prognostic role apart from ventricular arrhythmia and myocardial insufficiency. We refrained from an evaluation of the degree of coronary insufficiency on the electrocardiographic pattern because of the accepted difficulties of evaluating ST changes after previous acute myocardial infarction and also as the changes seen may be influenced by cardiotropic therapy.

Conclusions

We found that routine exercise tests 3 weeks and 9 weeks after an acute myocardial infarct give valuable prognostic information using the following measures: substantially increased heart rates, angina pectoris, and major ventricular arrhythmias. The exercise tests disclose a larger risk group than an ordinary resting electrocardiogram recorded on the same occasion. We consider that these early exercise tests, owing to the possibilities of standardisation and supervision, are a useful method for investigating the therapeutic and physical exercise management of these patients. Further studies are, however, required for the evaluation of the effect of antiarrhythmic therapy as well as treatment aimed at those symptoms found to be related to a worsened prognosis in these patients.

References

Coronary Drug Project Research Group (1973). Prognostic importance of premature beats following myocardial infarction. *Journal of the American Medical Association,* **223,** 1116–1124.

Crawford, M., O'Rourke, R. A. Ramakrishna, N., Henning, H., and Ross, J., Jr. (1974). Comparative effectiveness of exercise testing and continuous monitoring for detecting arrhythmias in patients with previous myocardial infarction. *Circulation,* **50,** 301–305.

Ericsson, M., Granath, A., Ohlsén, P., Södermark, T., and Volpe, U. (1973). Arrhythmias and symptoms during treadmill testing three weeks after myocardial infarction in 100 patients. *British Heart Journal,* **35,** 787–790.

Helmers, C. (1973). Short and long-term prognostic indices in acute myocardial infarction. *Acta Medica Scandinavica,* Suppl. 555.

Kentala, E., Pyörälä, K., Heikkilä, J., Sarna, S., and Luurila, U. (1975). Factors related to long-term prognosis following acute myocardial infarction. *Scandinavian Journal of Rehabilitation Medicine,* **7,** 118–124.

Kosowsky, B. D., Lown, B., Whiting, R., and Guiney, T. (1971) Occurrence of ventricular arrhythmias with exercise as compared to monitoring. *Circulation,* **44,** 826–832.

Kotler, M. N., Tabatznik, B., Mower, M. M., and Tominaga, S. (1973). Prognostic significance of ventricular ectopic beats with respect to sudden death in the late postinfarction period. *Circulation,* **47,** 959–966.

Lown, B., and Wolf, M. (1971). Approaches to sudden death from coronary heart disease. *Circulation,* **44,** 130–142.

Rehnqvist, N. (1976). Ventricular arrhythmias prior to discharge after acute myocardial infarction. *European Journal of Cardiology,* **4,** 63–70.

Ryan, M., Lown, B., and Horn, H. (1975). Comparison of ventricular ectopic activity during 24-hour monitoring and exercise testing in patients with coronary heart disease. *New England Journal of Medicine,* **292,** 224–229.

Shanoff, H. M, Little, J. A., Csima, A., and Yano, R. (1966). Studies of male survivors of myocardial infarction. *American Journal of Cardiology,* **18,** 535–539.

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Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction[1]

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The purpose of this study was to determine whether the early analysis of the electrocardiogram in patients with acute myocardial infarction may be useful in predicting the development of myocardial necrosis. It is based on observations in the dog that epicardial ST segment elevations (ST ↑) consequent to experimental coronary artery occlusion predict the development of myocardial necrosis, as judged by histological appearance, electron microscopy, myocardial creatine kinase activity, as well as the development of new Q waves and the decline of R waves in epicardial leads. Accordingly, the usefulness of early ST ↑ in the standard 12-lead electrocardiogram as a predictor of the subsequent development of electrocardiographic signs of necrosis was assessed. Studies were made on 51 patients with acute myocardial infarction who were admitted to the hospital within 8 hours of the onset of chest pain. Each QRS complex was scored from 0 to 4 as follows: 0=normal QRS; 1=fall in R wave amplitude by at least 0·2 mV and 50 per cent of control; 2=$Q\geq0{\cdot}2$ mV in depth and $\geq0{\cdot}04$ s in duration, but $Q<R$; 3=same as score 2 but $Q>R$; and 4=QS. Leads considered to be vulnerable for the development of necrosis were those with a score of 0 or 2 with ST ↑ $\geq0{\cdot}15$ mV on admission. Changes in score ≥2 occurred within 5 days in an average of $70{\cdot}4\pm4{\cdot}5$ per cent (SEM) of the vulnerable leads in the 68 vulnerable leads in the 27 patients with diaphragmatic myocardial infarction and in an average of $56{\cdot}7\pm7{\cdot}5$ per cent of the 76 vulnerable leads in 24 patients with anterior myocardial infarction (leads V1 to V6). The sum of the height of R waves (ΣR) in the vulnerable leads fell by $63{\cdot}7\pm3{\cdot}8$ per cent in patients with diaphragmatic myocardial infarction and $76{\cdot}1\pm4{\cdot}9$ per cent in patients with anterior myocardial infarction. Approximately four-fifths of the fall in ΣR and of score changes ≥2 which had occurred by the fifth day had already developed one day after admission.

It is concluded that there is a predictable percentage of leads with ST ↑ elevations in the initial electrocardiographic recordings, which ultimately develop signs of necrosis. A significant reduction in this percentage after a therapeutic intervention may be indicative of the sparing of jeopardised myocardium, and thus may provide a much needed approach to assessing the effects of interventions on the extent of myocardial necrosis.

The concept that the size of a myocardial infarct can be modified in experimental animals after coronary occlusion has gained support from studies using the method of epicardial ST segment mapping, correlated with analyses of creatine kinase (CK) activity and histological appearance of myocardial biopsies (Maroko *et al.*, 1971, 1972b; Maroko and Braunwald, 1973; Braunwald and Maroko, 1974; Hirshfeld *et al.*, 1974; Epstein *et al.*, 1975). In addition, the fact that the size of experimentally produced infarcts can be limited has been shown by a method totally independent of epicardial ST segment mapping. Histological analysis of the posterior papillary muscle after occlusion of the circumflex coronary artery has shown a reduction in necrosis in animals receiving propranolol (Reimer *et al.*, 1973) or mannitol (Reimer *et al.*, 1975). Thus, limitation of infarct size in animals has now been documented by two totally unrelated techniques. The potential clinical importance of these findings has been heightened by laboratory evidence that the quantity of myocardium which can

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be salvaged by these interventions is substantial and that it is possible to start treatment a number of hours after occlusion which will still be effective (Maroko *et al.*, 1972a; Maroko and Braunwald, 1973).

The salvage of contractile tissue otherwise destined to undergo necrosis may be expected to reduce the incidence of heart failure and ultimately of the mortality secondary to myocardial infarction (Harnarayan *et al.*, 1970; Scheidt *et al.*, 1970; Page *et al.*, 1971; Dizadji *et al.*, 1972). One of the most formidable barriers to the clinical application of this concept is the lack of a suitable technique to assess the efficacy, or lack thereof, of these interventions designed to accomplish this salvage. Specifically, a technique is needed which can be applied to patients at an early stage in the course of an infarction, when the injury to considerable quantities of myocardium is still in the reversible phase, which will predict the ultimate amount of myocardial necrosis to be anticipated, and which can then be repeated at a later time to assess the amount of damage which has actually occurred.

One technique that has been employed is the analysis of the rate of fall of ST segment elevation in the epicardial or praecordial electrocardiograms (Maroko *et al.*, 1971; Redwood *et al.*, 1972; Maroko and Braunwald, 1973; Braunwald and Maroko, 1974; Reid *et al.*, 1974; Borer *et al.*, 1975; Come *et al.*, 1975; Epstein *et al.*, 1975; Flaherty *et al.*, 1975; Maroko *et al.*, 1975); this method has the advantage of showing practically instantaneous changes in reversible tissue damage, thus making it possible to monitor increases or reductions of myocardial ischaemic injury (Maroko *et al.*, 1972a). This property, together with the simplicity and rapidity of the method, makes it suitable for the rapid evaluation of the effect of treatment of ischaemic injury. ST segment mapping, however, does *not* provide an absolute measurement of the size of the ischaemic zone. In addition, it is critical to recognise that factors other than ischaemia can affect the height of the ST segment. These include, but are not limited to, alterations in *p*H and ion concentrations, temperature changes, drugs such as quinidine and digitalis, the development of localised intraventricular conduction defects, and epicardial injury caused by pericarditis and myocardial injury not of ischaemic origin. Consequently, it would be misleading automatically to attribute changes in ST segments exclusively to alterations caused by ischaemia.

It has become clear from animal experiments (Radvany *et al.*, 1975; Hillis *et al.*, 1976) that epicardial sites which show ST segment elevation shortly after coronary occlusion have a predictable progression to QRS configurations indicative of necrosis (R wave fall and Q wave development). Interventions which have been shown to protect ischaemic myocardium by diminishing both CK depletion and the development of histological evidence of necrosis, reduce this fall of R wave and Q wave development.

The present investigation was undertaken to determine whether these concepts could be extended to the clinical sphere and specifically to ascertain whether in patients with acute myocardial infarction early ST segment elevations recorded in the 12 standard leads can be used to predict the subsequent development of electrocardiographic signs of necrosis, as reflected in the appearance of pathological Q waves and fall in R wave voltages in the same leads.

Methods

The electrocardiograms of 51 consecutive patients with acute myocardial infarctions admitted to the Peter Bent Brigham Hospital whose electrocardiograms satisfied the following criteria were analysed:

1. Acute myocardial infarction diagnosed by a typical history, typical electrocardiographic pattern of an acute transmural myocardial infarction by ST-T wave changes, and increases in serum CK, LDH, and SGOT activities to at least 3 times the upper limits of normal.
2. Availability of an electrocardiogram recorded within 8 hours of the onset of pain (ECG_0) in which at least one of the leads (other than aVR) showed both an ST segment elevation $\geq 0{\cdot}15$ mV and a score of 0 or 2 in the same lead (for definition of score see below). Thus, the electrocardiographic criteria require the existence of ST segment elevations independent of existence of Q waves and the existence in the same leads of QRS complexes that could undergo further necrosis.
3. Availability of electrocardiograms recorded 1 day (ECG_{1d}) and 5 days (ECG_{5d}) after admission.

Patients with intraventricular conduction defects, bundle-branch block, hemiblock, and third degree atrioventricular block were excluded.

The patients consisted of 43 men and 8 women who averaged $60{\cdot}2 \pm 11{\cdot}8$ years (SD) in age. The time from the onset of pain to the first electrocardiogram averaged $4{\cdot}7 \pm 2{\cdot}1$ hours (SD).

In order to examine the evolution of the QRS complex throughout the first days after acute myocardial infarction the 3 electrocardiograms (i.e. ECG_0, ECG_{1d}, and ECG_{5d}) were analysed as follows:

(1) QRS 'SCORES'

The QRS complexes were scored from 0 to 4 regardless of abnormalities of the ST segment or the T waves (Fig. 1) as follows: (i) A score of *0* represented a QRS with normal appearance, i.e. Q wave $<0{\cdot}2$ mV and/or <40 ms; (ii) a score of *1* represented a decline in R wave amplitude by $\geq 0{\cdot}2$ mV and ≥ 50 per cent from that recorded in ECG_0; the Q wave remained $<0{\cdot}2$ mV and <40 ms; (iii) a score of *2* represented a complex with Q wave amplitude of $\geq 0{\cdot}2$ mV, duration of ≥ 40 ms and a $Q/R \leq 1{\cdot}0$; (iv) a score of *3* represented a complex identical to that defined for a score of 2, except that $Q/R > 1{\cdot}0$; (v) a score of *4* represented a QS complex.

In the initial tracing (ECG_0) leads having ST segment elevations $\geq 0{\cdot}15$ mV and score of 0 or 2 were considered to be vulnerable for the development of necrosis. The percentage of such leads in which the scores increased by more than 1 or 2 in ECG_{1d} and ECG_{5d} were determined.

(2) ANALYSIS OF FALL IN HEIGHT OF R WAVES

R wave heights were measured in all vulnerable sites, as defined above, and the change in the sum of R waves (ΣR) in all vulnerable sites, in ECG_{1d} and ECG_{5d}, in each patient was determined and expressed both in mV and as a percentage of the ΣR in ECG_0.

In patients with a diaphragmatic wall myocardial infarction (group 1, 27 patients), these analyses were carried out both in lead aVF alone and in leads II, III, and aVF considered together. In patients with acute anterior myocardial infarction only leads V1 through V6 (group 2, 24 patients) were analysed. Comparisons of ECG_0 and ECG_{1d} and of ECG_0 and ECG_{5d} were made using Student's t test for paired observations (Snedecor and Cochran, 1967).

Results

GROUP 1

The 27 patients with diaphragmatic wall myocardial infarction in whom the standard unipolar and bipolar leads (II, III, and aVF) were analysed (Fig. 2) had 68 vulnerable leads. The percentage of vulnerable leads per patient which showed a change in score ≥ 1 averaged $60{\cdot}5 \pm 7{\cdot}9$ per cent (SEM) at day 1 and $74{\cdot}1 \pm 6{\cdot}7$ per cent at day 5 (Fig. 3) while for a change in score ≥ 2 these values averaged $56{\cdot}7 \pm 6{\cdot}0$ per cent at day 1 and $70{\cdot}4 \pm 4{\cdot}5$ per cent at day 5 (Fig. 4). The ΣR in vulnerable sites averaged $1{\cdot}83 \pm 0{\cdot}22$ mV per patient in ECG_0 and had declined by an average of $0{\cdot}93 \pm 0{\cdot}15$ mV (i.e. $50{\cdot}8 \pm 4{\cdot}2\%$) at day 1 and by $1{\cdot}15 \pm 0{\cdot}81$ mV (i.e.

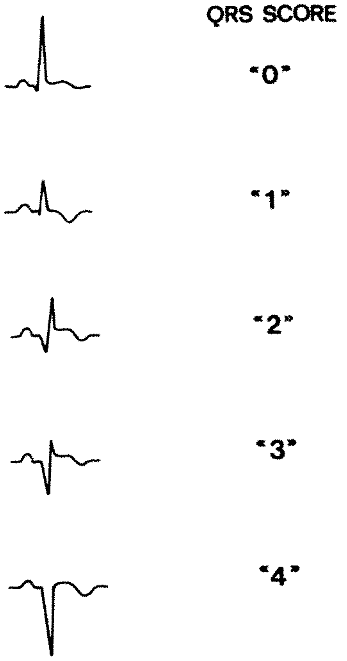

Fig. 1 *Method of QRS scoring, as described in the text.*

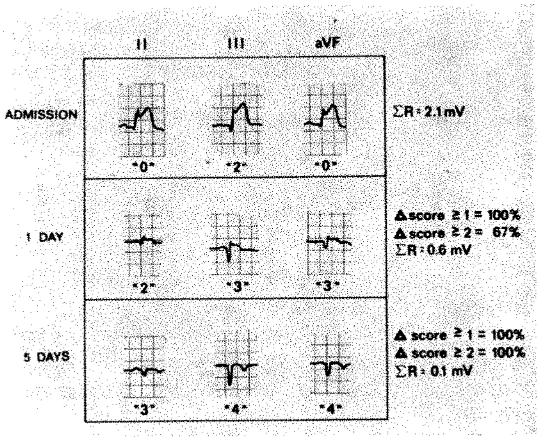

Fig. 2 *Electrocardiogram from a patient with an acute diaphragmatic myocardial infarct. Leads II, III, and aVF on admission are considered to be vulnerable sites, as defined in the text, since in each, ST segment elevation $\geq 0{\cdot}15$ mV and the score does not exceed 2. Twenty-four hours later all 3 leads (100%) evolved a change of score ≥ 1, and 2 of the 3 leads (67%), i.e. II and aVF developed a change in score ≥ 2. By 5 days all 3 leads changed score ≥ 2. ΣR fell by 1·5 mV (71%) in 1 day and by 2·0 mV (95%) in 5 days.*

63·7 ±3·8%) at day 5 (Fig. 5).

In the 27 patients with diaphragmatic wall myocardial infarction, lead aVF alone was also analysed. In 20 of these 27 vulnerable leads (74·1%) exhibited a change of score ≥1 at day 1 and 96·3 per cent at day 5. The comparable values for changes in score ≥2 were 63·0 per cent at day 1 and 77·8 per cent at day 5. The R wave voltage in these 27 vulnerable leads averaged 0·61 ±0·09 mV and it declined by an average of 0·32 ±0·06 (i.e. 56·1 ± 6·5%) at day 1 and by 0·41 ±0·07 mV (i.e. 70·1 ± 5·5%) at day 5.

GROUP 2

The 24 patients with anterior myocardial infarction in whom the standard praecordial leads (V1–V6) were analysed had 76 vulnerable sites (Fig. 6). The percentage of vulnerable leads per patient which showed a change in score ≥1 averaged 61·7 ±8·2 per cent at day 1 and 80·8 ±4·5 per cent at day 5 (Fig. 3 and Table), while for a change in score ≥2 these values averaged 31·5 ±7·4 per cent at day 1 and 56·7 ±7·5 per cent at day 5 (Fig. 4 and Table). The ΣR in the vulnerable leads averaged 2·01 ± 0·48 mV per patient in ECG_0 and declined by an average of 1·22 ± 0·38 mV (i.e. 55·8 ± 6·2%) at day 1 and by 1·40 ± 0·40 mV (i.e. 76·1 ± 4·9%) at day 5 (Fig. 5 and Table).

Discussion

Both experimental and clinical pathological studies carried out during the past 40 years have shown a correlation between changes in the QRS complex and the extent of myocardial necrosis in patients and experimental animals with coronary occlusion. Wilson *et al.* (1933) noted the development of QS complexes in epicardial leads as indicators of transmural myocardial necrosis. Prinzmetal *et al.*

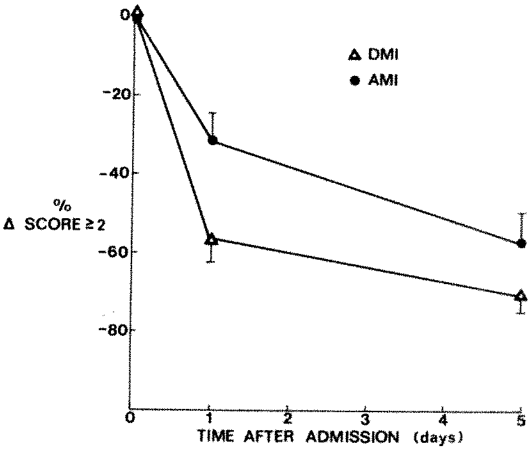

Fig. 4 *Average (±SEM) per cent of vulnerable sites per patient which changed in score ≥2 in 1 and 5 days after admission in 27 patients with diaphragmatic wall myocardial infarction (DMI, triangles) and in 24 patients with anterior myocardial infarction (AMI, circles).*

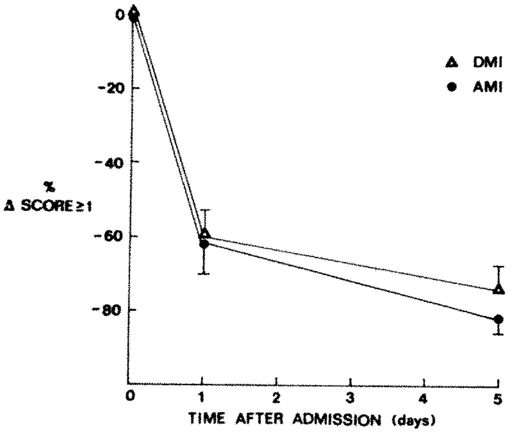

Fig. 3 *Average (±SEM) per cent of vulnerable sites per patient which changed in score ≥1 in 1 and 5 days after admission in 27 patients with diaphragmatic wall infarcts (DMI, triangles) and in 24 patients with anterior myocardial infarction (AMI, circles). Of the changes occurring on the fifth day approximately four-fifths had already occurred by the first day.*

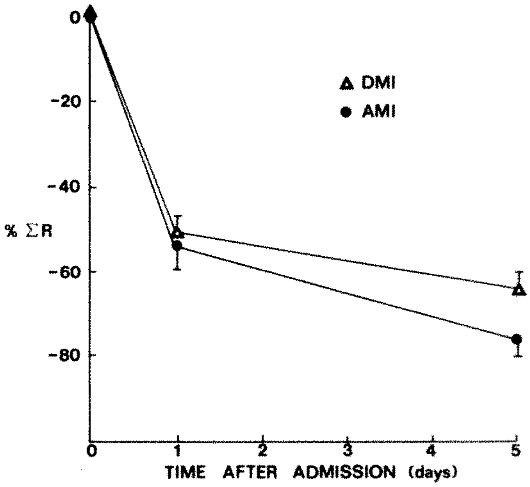

Fig. 5 *Per cent fall in the sum of R waves (ΣR) in vulnerable sites in patients with acute diaphragmatic wall myocardial infarction (DMI, triangles) and in the 24 patients with acute anterior myocardial infarction (AMI, circles).*

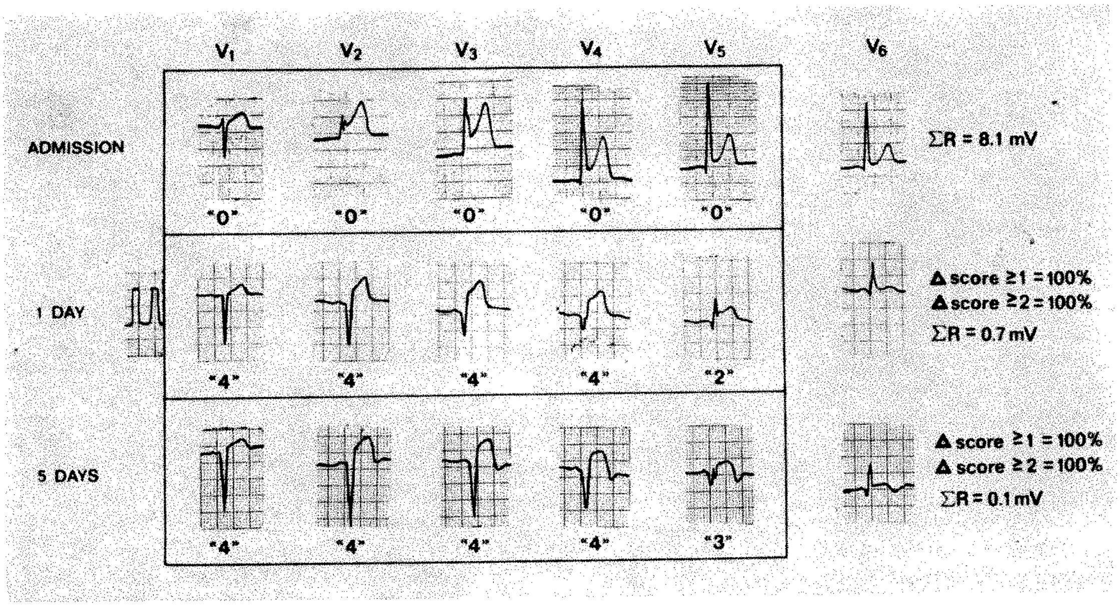

Fig. 6 *Praecordial leads V1 to V6 from a patient with acute anterior myocardial infarction. Five of these leads (V1–V5) are considered to be vulnerable to the development of electrocardiographic signs of necrosis. The scores are indicated below each tracing. Within one day all 5 sites (100%) have changed score by 2 or more. ΣR fell by 91 per cent of control* $\frac{8\cdot1\ mV - 0\cdot7\ mV}{8\cdot1\ mV}$ *in the first day and by 99 per cent in 5 days.*

(1954) and Shaw *et al.* (1954) analysed the origin of the QS complex in detail. They pointed out that the outer layers of the myocardium were ordinarily responsible for the R wave and stated that 'death of muscle in the outer ventricular layers eliminates or reduces the magnitude of the positive epicardial potential'. These investigators also observed that a QR pattern in epicardial leads might reflect the presence of a mixture of viable and necrotic myocardial cells.

Wilson *et al.* (1944) suggested that praecordial electrocardiograms provided information concerning the portion of the myocardium closest to the exploring electrode and termed these leads 'semidirect leads'. Extensive clinico-pathological correlations were then carried out by Myers *et al.*, who established the relation between electrocardiographic abnormalities in particular leads and the occurrence of infarction in specific areas of the myocardium (Myers *et al.*, 1948a, b; 1949a, b, c).

More recently, the relation between the appearance of new Q waves, the fall in R waves, and the development of myocardial necrosis were re-examined in our laboratory (Radvany *et al.*, 1975;

Table *Alterations in QRS complex in 5 days—anterior myocardial infarction*

Case No.	$\% \downarrow \Sigma R_{5d}$	$\% \Delta score \geq 1_{5d}$	$\% \Delta score \geq 2_{5d}$
1	35	67	0
2	48	60	25
3	67	50	0
4	100	100	50
5	100	100	100
6	100	100	100
7	100	100	100
8	87	100	50
9	93	100	75
10	100	100	50
11	100	100	100
12	43	67	67
13	96	75	66
14	100	100	100
15	80	50	50
16	56	100	100
17	98	67	67
18	46	50	0
19	76	100	20
20	42	33	0
21	46	67	33
22	68	100	100
23	97	86	75
24	50	67	33
Mean	76·1	80·8	56·7
SD	24·0	20·9	36·5
SE	4·9	4·4	7·5

Hillis *et al.*, 1976). Studies in dogs 24 hours after an experimentally produced coronary occlusion showed a highly significant correlation between the development of epicardial Q waves, the diminution of R wave voltages, and depression of myocardial creatine kinase (CK) activity and the histological appearance of myocardial infarction at the corresponding epicardial sites. Moreover, it was shown that epicardial ST segment elevation shortly after coronary occlusion accurately predicts the extent of subsequent myocardial infarction, as reflected in the reduction of myocardial CK activity, in the histological appearance of the myocardium as well as in the changes in the QRS complex (Hillis *et al.*, 1976). In other studies we observed that ST segment elevations, both in praecordial and epicardial leads, correlate well with the subsequent development of myocardial necrosis (Muller *et al.*, 1975).

One of the major objectives of the present study was to provide a quantitative description of the evolution of the QRS complex in patients with acute myocardial infarction. However, the aim of this study was not to determine the rate of fall of R wave or the appearance of pathological Q waves. Rather, the principal finding is that within 5 days of admission approximately two-thirds of the leads which present with ST segment elevations $\geq 0{\cdot}15$ mV within 8 hours after the onset of chest pain develop electrocardiographic signs of necrosis, as reflected in the development of new, pathological Q waves ($\geq 0{\cdot}2$ mV and ≥ 40 ms). These leads also develop striking reductions in the R wave, i.e. reductions of the order of 70 per cent. The incidence of these changes were similar in leads II, III, and aVF in patients with diaphragmatic wall infarcts, and in the praecordial leads V1 through V6 in patients with anterior myocardial infarction. In the former group, the analysis of aVF alone or II, III, and aVF provided similar results, suggesting that even when only one lead is analysed the progression of the necrotic process can be assessed.

To apply this approach clinically, we propose to use the praecordial ST segment recorded as early as possible after the onset of the clinical event as a predictor of the ultimate fate of the tissue in a manner analogous to the epicardial ST segment in the experimental animal. This praecordial ST segment may then be compared with the changes in the QRS complex that occur subsequently, such as the development or deepening of Q waves and the reduction of R waves; these changes in the QRS complex could be employed in a manner analogous to the alterations in CK activity or histological appearance of the myocardium subjacent to the epicardial electrode in the experimental animal. It should be emphasised, however, that this group of patients should not be used as a control group for future studies but rather during each investigation the patients should be randomised into control and treated groups and the evolutive QRS changes compared.

Before applying this method clinically, it was necessary to obtain a clear picture of the natural evolution of changes in the QRS complex in patients with acute myocardial infarction who had no treatment to protect ischaemic myocardium. The present study provides this picture; it indicates that the evolution of the QRS complex is quite predictable and that there is relatively little variability in the extent of electrocardiographic changes occurring in the vulnerable sites with transmural myocardial infarction when the initial tracing is obtained less than 8 hours after the onset of the clinical event. If, with the application of an intervention, the decline in ΣR and the change in score occurring in vulnerable sites were significantly less than in a comparable group of control patients, it would be consistent with a beneficial effect.

The proposed simultaneous analysis of the ST segment and QRS wave alterations, while not capable of expressing the mass of infarcted myocardium in quantitative terms, appears to be: (1) capable of predicting the surface representation of the extent of necrosis to be expected when much of the myocardial injury is still in a reversible phase, i.e. at a time of ST segment elevation, before the development of changes in the QRS complex; (2) capable of assessing the surface representation of the extent of necrosis that actually develops, as reflected in the change in the QRS complex; (3) capable of being applied immediately, i.e. without requiring any delay in therapy; (4) safe and atraumatic; and (5) simple to apply, easy to interpret, and inexpensive.

References

Borer, J. S., Redwood, D. R., Levitt, B., Cagin, N., Bianchi, C., Vallin, H., and Epstein, S. E. (1975). Reduction in myocardial ischemia with nitroglycerin or nitroglycerin plus phenylephrine administered during acute myocardial infarction. *New England Journal of Medicine*, **293**, 1008–1012.

Braunwald, E., and Maroko, P. R. (1974). The reduction of infarct size—an idea whose time (for testing) has come. *Circulation*, **50**, 206–209.

Come, P. C., Flaherty, J. T., Baird, M. G., Rouleau, J. R., Weisfeldt, M. L., Greene, H. L., Becker, L., and Pitt, B. (1975). Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction. *New England Journal of Medicine* **293**, 1003–1007.

Dizadji, H., Nissen, R., Mathew, M., Hoesley, J. B., and Cernock, W. (1972). Myocardial infarction. Mortality factors in coronary care units. *Geriatrics*, **27**(12), 76–86.

Epstein, S. E., Kent, K. M., Goldstein, R. E., Borer, J. S., and Redwood, D. R. (1975). Reduction of ischemic injury by nitroglycerin during acute myocardial infarction. *New England Journal of Medicine,* **292,** 29–35.

Flaherty, J. T., Reid, P. R., Kelly, D. T., Taylor, D. R., Weisfeldt, M. L., and Pitt, B. (1975). Intravenous nitroglycerin in acute myocardial infarction. *Circulation,* **51,** 132–139.

Harnarayan, C., Bennett, M. A., Pentecost, B. L., and Brewer, D. B. (1970). Quantitative study of infarcted myocardium in cardiogenic shock. *British Heart Journal,* **32,** 728–732.

Hillis, L. D., Askenazi, J., Braunwald, E., Radvany, P., Muller, J. E., Fishbein, M. C., and Maroko, P. R. (1976). Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion. *Circulation,* **54,** 591–598.

Hirshfeld, J. W., Jr., Borer, J. S., Goldstein, R. E., Barrett, M. J., and Epstein, S. E. (1974). Reduction in severity and extent of myocardial infarction when nitroglycerin and methoxamine are administered during coronary occlusion. *Circulation,* **49,** 291–297.

Maroko, P. R., and Braunwald, E. (1973). Modification of myocardial infarction size after coronary occlusion. *Annals of Internal Medicine,* **79,** 720–733.

Maroko, P. R., Davidson, D. M., Libby, P., Hagan, A. D., and Braunwald, E. (1975). Effects of hyaluronidase administration on myocardial ischemic injury in acute infarction. A preliminary study in 24 patients. *Annals of Internal Medicine,* **82,** 516–520.

Maroko, P. R., Kjekshus, J. K., Sobel, B. E., Watanabe, T., Covell, J. W., Ross, J., Jr., and Braunwald, E. (1971). Factors influencing infarct size following experimental coronary artery occlusions. *Circulation,* **43,** 67–82.

Maroko, P. R., Libby, P., Covell, J. W., Sobel, B. E., Ross, J., Jr., and Braunwald, E. (1972a). Precordial S-T segment elevation mapping: an atraumatic method for assessing alterations in the extent of myocardial ischemic injury. The effects of pharmacologic and hemodynamic interventions. *American Journal of Cardiology,* **29,** 223–230.

Maroko, P. R., Libby, P., Sobel, B. E., Bloor, C. M., Sybers, H. D., Shell, W. E., Covell, J. W., and Braunwald, E. (1972b). Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. *Circulation,* **45,** 1160–1175.

Muller, J. E., Maroko, P. R., and Braunwald, E. (1975). Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischemic injury. *Circulation,* **52,** 16–27.

Myers, G. B., Klein, H. A., and Hiratzka, T. (1948a). II. Correlation of the electrocardiographic and pathologic findings in large anterolateral infarcts. *American Heart Journal,* **36,** 838–881.

Myers, G. B., Klein, H. A., and Hiratzka, T. (1949a). III. Correlation of electrocardiographic and pathologic findings in anteroposterior infarction. *American Heart Journal,* **37,** 205–236.

Myers, G. B., Klein, H. A., and Hiratzka, T. (1949b). IV. Correlation of electrocardiographic and pathologic findings in infarction of the interventricular septum and right ventricle. *American Heart Journal,* **37,** 720–770.

Myers, G. B., Klein, H. A., and Stofer, B. E. (1948b). I. Correlation of electrocardiographic and pathologic findings in anteroseptal infarction. *American Heart Journal,* **36,** 535–575.

Myers, G. B., Klein, H. A., and Stofer, B. E. (1949c). VII. Correlation of electrocardiographic and pathologic findings in lateral infarction. *American Heart Journal,* **37,** 374–417.

Page, D. L., Caulfield, J. B., Kastor, J. A., DeSanctis, R. W., and Sanders, C. A. (1971). Myocardial changes associated with cardiogenic shock. *New England Journal of Medicine,* **285,** 133–137.

Prinzmetal, M., Kennamer, R., and Maxwell, M. (1954). Studies on the mechanism of ventricular activity. VIII. The genesis of the coronary QS wave in through-and-through infarction. *American Journal of Medicine,* **17,** 610–613.

Radvany, P., Askenazi, J., Maroko, P. R., and Braunwald, E. (1975). Predictive value of ST segment in the development of electrocardiographic signs of necrosis after experimental coronary artery occlusion. *Circulation,* **52,** Suppl. II, II-6.

Redwood, D. R., Smith, E. R., and Epstein, S. E. (1972). Coronary artery occlusion in the conscious dog. Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia. *Circulation,* **46,** 323–332.

Reid, P. R., Taylor, D. R., Kelly, D. T., Weisfeldt, M. L. Humphries, J. O., Ross, R. S., and Pitt, B. (1974). Myocardial-infarct extension detected by precordial ST-segment mapping. *New England Journal of Medicine,* **290,** 123–128.

Reimer, K. A., Kloner, R. A., Willerson, J. T., and Jennings, R. B. (1975). Reduction of infarct size by mannitol during acute myocardial ischemia. *Circulation,* **52,** Suppl. II, II-64.

Reimer, K. A., Rasmussen, M. M., and Jennings, R. B. (1973). Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. *Circulation Research,* **33,** 353–363.

Scheidt, S., Ascheim, R., and Killip, T., III. (1970). Shock after acute myocardial infarction. A clinical and hemodynamic profile. *American Journal of Cardiology,* **26,** 556–564.

Shaw, C. McK., Goldman, A., Kennamer, R., Kimura, N., Lindgren, I., Maxwell, M. H., and Prinzmetal, M. (1954). Studies on the mechanism of ventricular activity. VII. The origin of the coronary QR wave. *American Journal of Medicine,* **16,** 490–503.

Snedecor, G. W., and Cochran, W. G. (1967). *Statistical Methods,* 6th ed. The Iowa State University Press, Ames.

Wilson, F. N., Johnston, F. D., Rosenbaum F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S. (1944). The precordial electrocardiogram. *American Heart Journal,* **27,** 19–85.

Wilson, F. N., MacLeod, A. G., Barker, P. S., Johnston, F. D., and Klostermeyer, L. L. (1933). The electrocardiogram in myocardial infarction with particular reference to the initial deflections of the ventricular complex. *Heart,* **16,** 155–176.

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Indirect measurement of sinoatrial conduction time in patients with sinoatrial disease and in controls

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Clinical recognition of sinoatrial disease currently depends on the presence of transient sinus bradycardia, sinoatrial block, or supraventricular tachyarrhythmias. The value of clinical electrophysiological assessment in these patients is not clear. Using intracardiac electrophysiological recordings and programmed stimulation we have examined 14 patients with sinoatrial disease and 11 control patients undergoing investigation for chest pain.

Intracardiac conduction times were normal in all patients. There was no significant difference of sinus node recovery times between the sinoatrial disease and control groups. Sinoatrial conduction times were measured by the indirect method and two populations were identified. However, the mean values of 128±27 ms in patients and 112±30 ms in controls were not significantly different and major overlap rendered this measurement clinically valueless.

It is concluded that no current electrophysiological measurement has diagnostic value in patients with sinoatrial disease.

Patients with sinoatrial disease have various arrhythmias which are, most commonly, sinoatrial block or sinus arrest, sinus bradycardia, and supraventricular tachycardias (Greenwood and Finkelstein, 1964; Bouvrain *et al.*, 1967). The diagnosis of this condition has depended on recognition of the characteristic arrhythmias which are frequently transient and may not be apparent on routine electrocardiography (Crook *et al.*, 1973). The need has remained for a reproducible measure of sinus node function or of sinoatrial conduction which might identify patients with this condition.

Among attempts to evaluate sinus node function, overdrive suppression has proved to be of limited value since a majority of patients with sinoatrial disease may show results within the normal range (Gupta *et al.*, 1974). A technique for measuring sinus node depression after single and progressively more premature atrial depolarisations was described by Goldreyer and Damato in 1971. The same technique was used by Strauss and colleagues in 1973 as an indirect measure of sinoatrial conduction time rather than as an index of sinus node depression. Sinoatrial conduction time was measured by the difference between the basic sinus cycle length and the atrial recovery time, when paced atrial premature depolarisations in the earlier part of atrial diastole resulted in a constant recovery interval caused by reset of the sinus node.

In practice, however, conflicting results have been obtained concerning the value of this test for the identification of patients with sinoatrial disease (Hirschfeld *et al.*, 1975; Masini *et al.*, 1975). It has also been suggested that indirect sinoatrial conduction time must be corrected for the basic sinus cycle length (Reiffel *et al.*, 1974). However, the relation of sinoatrial conduction time to the basic sinus cycle length has not been fully examined.

We have attempted to measure sinoatrial conduction time by the indirect method in a group of patients with the characteristic arrhythmias of sinoatrial disease and in a comparable control group with no known arrhythmias. We have also investigated the relation between sinoatrial conduction time and basic sinus cycle length in order to determine whether correction for basic cycle length would be appropriate.

Patients and methods

Sinoatrial conduction time and sinus node recovery time were measured in each of 25 patients, 14 of

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Table 1 *Electrocardiographic and electrophysiological details of the 14 patients with sinoatrial disease*

Age (y)	*Sex*	*Electrocardiogram*			*Distribution of normalised return against test cycles*	*Sinus node recovery time (ms)*	*Sinoatrial conduction time (ms)*
		Sinus bradycardia	*Sinoatrial block*	*Supraventricular tachycardias*			
72	M	40/min	+	—	Chaotic	720	—
67	M	—	+	—	Linear	1080	—
45	F	48	—	+	Normal	980	123
27	F	54	+	+	Linear	710	—
40	F	38	+	+	Normal	920	113
73	M	50	+	—	Chaotic	1010	—
25	F	48	+	+	Chaotic	1450	—
51	F	50	+	—	Normal	740	122
60	F	—	+	—	Normal	870	134
71	M	44	—	+	Normal	1150	101
41	M	48	+	+	Normal	1080	135
38	M	50	+	+	Chaotic	1540	—
35	F	—	+	+	Normal	985	172
46	F	—	+	+	Normal	850	125
Means and standard deviation						1006 + 249	128 + 27

whom suffered from typical sinoatrial disease (Table 1). The patients with sinoatrial disease were all symptomatic and had at least 2 of the 3 characteristic arrhythmias, sinus bradycardia, sinoatrial block, or supraventricular tachyarrhythmias. The other 11 patients (Table 2) were 'controls' suffering from chest pain but no known arrhythmias, and these were investigated with electrophysiological studies at the time of coronary arteriography. All patients had given informed written consent and none had received previous sedation or antiarrhythmic drugs within 2 weeks of the investigation.

Quadripolar and bipolar electrodes were inserted percutaneously into the right femoral vein. The quadripolar electrode was positioned at the upper right atrium using the distal pair of electrodes for programmed stimulation and the proximal pair of electrodes for sensing and recording spontaneous right atrial activity. Simultaneous records of the His bundle were obtained from the bipolar electrode together with surface electrocardiographic leads I, III, and V1. The atrioventricular (AH) and His-Purkinje (HV) conduction intervals were measured from these records.

Table 2 *Clinical and electrophysiological details of 11 control patients with chest pain*

Age (y)	*Sex*	*Coronary obstructions*	*Distribution of normalised return against test cycles*	*Sinus node recovery time (ms)*	*Sinoatrial conduction time (ms)*
62	M	+	Normal	880	85
32	M	+	Normal	640	81
44	M	—	Normal	1140	97
35	M	+	Normal	1110	154
42	M	+	Chaotic	820	—
44	F	—	Normal	920	100
56	M	+	Normal	740	116
59	M	+	Normal	830	138
47	M	+	Normal	830	126
57	M	+	Chaotic	1125	—
47	M	+	Normal	1100	121
Means and standard deviations				921 ± 172	112 ± 30

Sinus node recovery time was measured by pacing the atrium at a rate just below that producing Wenckebach periodicity, with pacing rates ranging from 60 to 170 beats a minute. After pacing for 30 seconds and switching off, the interval from the last paced atrial complex to the atrial recovery complex was measured.

Sinoatrial conduction time was measured by the method described by Strauss and colleagues (1973). The upper atrial signals were sensed and paced impulses introduced at predetermined intervals from the spontaneous beat with a programmable stimulator (Devices Ltd.). A pulse width of 2 ms was used and a voltage of 2 or 3 times the diastolic threshold. A single premature paced depolarisation was programmed to follow each eighth sensed sinus beat with a predetermined delay. This delay was increased for each paced beat with a 5 or 10 ms increment so that paced impulses were programmed to occur during the whole non-refractory part of the atrial cycle.

The following intervals were measured from the permanent records made with an 8-channel ink jet recorder (Mingograph).

Previous sinus cycle length (PC) was the interval between the last two spontaneous atrial beats before the paced impulse was introduced.

Test cycle length (TC) was the interval between the last spontaneous sinus beat and the paced impulse.

Return cycle length (RC) was the interval between the paced premature impulse and the subsequent returning spontaneous atrial beat.

The relation between the lengths of the test and return cycles was shown graphically for each patient. For the construction of these distributions the results were expressed in two ways. The return cycles were either first normalised as fractions of their corresponding basic (previous) sinus cycle lengths (i.e. $\frac{\mathrm{RC}}{\mathrm{PC}}$), or were plotted directly (without normalisation) against the test cycle lengths. The curve most commonly obtained (Fig. 1) shows a plateau zone where the earlier paced impulses have entered and reset the sinus node and a tail zone where the later paced impulses have fallen after the spontaneous sinus node depolarisation. In the tail zone, sinus node reset has not occurred so that the return cycles now become shorter and exactly compensatory. Calculation of sinoatrial conduction time was made from those values falling in the plateau zone of the curve. The atrial return cycles in this zone represent the time taken for the paced impulse to enter the sinus node from the atrium, the duration of the return sinus node cycle, and the time taken for the return sinus node impulse to enter and trigger the atrium. The sinus node return cycle after the paced impulse is assumed to be similar to the basic sinus cycle length (previous sinus cycle length). Hence by subtracting this value (PC) from the return cycle (RC), conduction time into and out of the sinus node can be calculated. This value is then halved to give an approximation to the sinoatrial conduction time (SACT). Expressed as a formula, $\mathrm{SACT} = \frac{\mathrm{RC-PC}}{2}$. A mean sinoatrial conduction time is calculated from all the return and previous cycles in the plateau zone of the graph.

A computer graph plot and sinoatrial conduction time calculations were made in this way for each patient studied.

The discriminative value of the sinoatrial conduction time results for the sinoatrial disease and control patients was then assessed (Student's t test).

To investigate the relation of sinoatrial conduction time to basic cycle length, the different sinoatrial conduction time values corresponding to all the points in the plateau zone were plotted against corresponding previous sinus cycle lengths so that a curve expressing the sinoatrial conduction time to previous sinus length relation was initially sought for each patient individually. In addition, a single composite curve was constructed for all the values from 17 of the patients in whom a clear plateau zone was obtained.

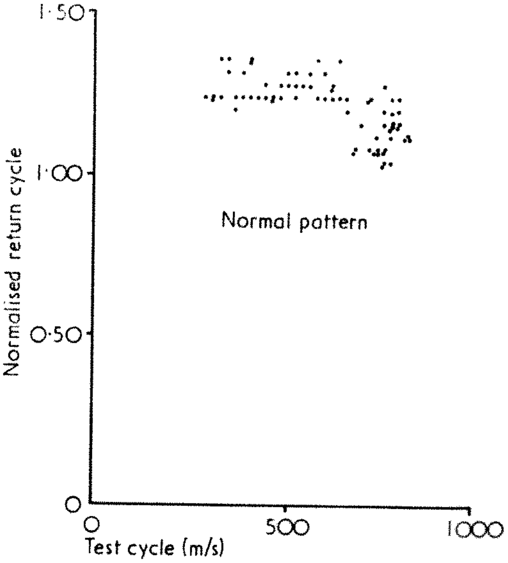

Fig. 1 *Distribution of normalised return* $\frac{RC}{PC}$ *against test cycle lengths. There is a plateau zone to the left and a tail zone to the right.*

Results

The atrioventricular (AH) and His-Purkinje (HV) conduction intervals were within normal limits in all

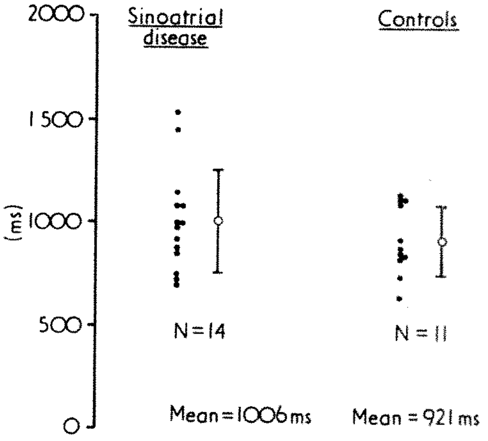

Fig. 2 *Sinus node recovery times in the patients with sinoatrial disease and the controls. The vertical bars represent the means and standard deviations.*

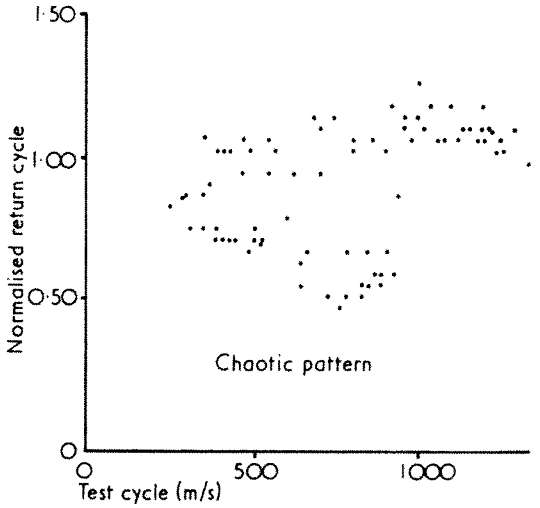

Fig. 3 *Distribution of normalised return against test cycle lengths to show a typical 'chaotic' pattern.*

from the patients included in this study.

Sinus node recovery time showed no significant difference between the sinoatrial disease and control patients though a small difference between the mean values for each group was observed (Fig. 2 and Tables 1 and 2).

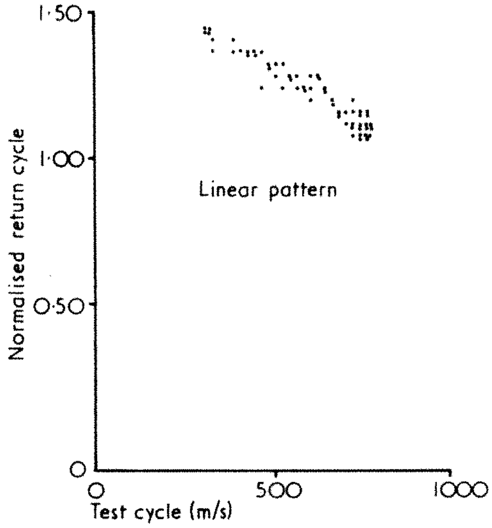

Fig. 4 *Distribution of normalised return against test cycle lengths to show a linear pattern.*

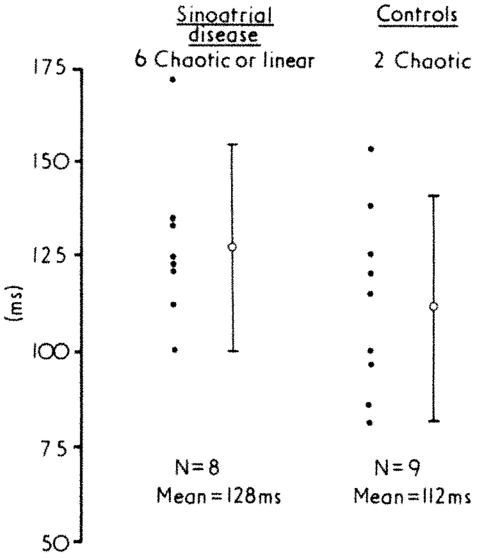

Fig. 5 *Sinoatrial conduction times in the patients with sinoatrial disease and the controls. The vertical bars represent the means and standard deviations.*

Sinoatrial conduction time could be measured satisfactorily in 17 of the 25 patients where clear plateau zones could be identified (Fig. 1) in the plots of the normalised return and test cycle lengths. In the remaining 8 patients a distinct plateau zone was not seen either because the plotted values showed a chaotic pattern (Fig. 3, 6 patients) or a linear prolongation of return cycles in response to decreasing test cycles (Fig. 4, 2 patients). Similar graphs of test against return cycles without normalisation were obtained and the same pattern of chaotic, linear, or plateau curves was found. Sinoatrial conduction time was calculated from the values in the plateau zone from both methods of plotting the original graphs, and similar values were obtained despite the differences in normalisation. The sinoatrial conduction time results for each patient are shown in Tables 1 and 2 and Fig. 5.

The sinoatrial conduction time mean values for the patients with sinoatrial disease did not differ significantly from the mean values obtained in the control patients.

The overall mean of the mean sinoatrial conduction time results for the 8 patients with sinoatrial disease was 128 ± 27 ms and for the 9 patients with chest pain was 112 ± 30 ms.

For the 17 patients with a clear plateau zone, no relation was found between sinoatrial conduction time and previous cycle length values when these were plotted for each patient individually. When all the values for these patients were put together for a composite plot a poor correlation was observed:

Sinoatrial conduction time = −(0·083 ± 0·1) previous sinus cycle length + 189 ± 8·6 with correlation coefficient of −0·33.

Discussion

Sinus node recovery time may be increased to some extent by an increased rate of pacing (Narula *et al.*, 1972). We chose to pace at a high rate before switch-off and accepted that pacing for 30 seconds might be adequate and avoid discomfort (Mandel *et al.*, 1971). Our results were similar to those of other workers in failing to discriminate between patients with sinoatrial disease and controls (Gupta *et al.*, 1974; Lee *et al.*, 1975).

The indirect measurement of sinoatrial conduction time, described by Strauss *et al.* (1973), necessitates construction of a graph to show the relation between test and return atrial cycles. Calculation of sinoatrial conduction time is made from values falling in the plateau zone of the curve which correspond to sinus node reset. For this graph, test and return cycle lengths have been plotted, either with both normalised as fractions of the basic sinus cycle length (Strauss *et al.*, 1973) or plotted directly against each other without normalisation (Reiffel *et al.*, 1974). Both basic sinus cycle length and return cycle length will be influenced in a similar way by autonomic and other factors, and if basic sinus cycle lengths (previous cycle length) are plotted against corresponding return cycle lengths the regression is approximately linear (Reiffel *et al.*, 1974). Hence in order to obtain a graphic demonstration of the relation of return to test cycle length and allow for the variation of return cycle length resulting from other physiological variables, we chose initially to normalise only the return cycles which were then plotted against direct values for test cycle lengths. However, plots were also made without normalisation.

The appearances of the graphs were similar in each of the 17 patients with or without normalisation of the return cycles, and similar values for sinoatrial conduction time resulted. However, less scatter of points occurred with normalisation of the return cycles.

In 8 of our 25 patients the plots of return against test cycles showed a linear or chaotic pattern and were unsuitable for the method of analysis described by Strauss and colleagues (1973). This problem was not observed by Goldreyer and Damato (1971) or Reiffel *et al.* (1974) though in some cases a linear prolongation of return cycle rather than a plateau zone was noted by Hirschfeld *et al.* (1975). The chaotic pattern was more common among our patients with sinoatrial disease than in the controls. Two separate populations of basic sinus cycle lengths have been observed in some patients with sinoatrial disease (Crook and Cashman, 1976) with frequent rate switching suggesting two primary pacemaker sites in the sinus node. This effect may be the same as that causing the variation of sinus and return cycle lengths in the patients with the chaotic response pattern. A linear pattern could be explained if conduction from sinus node to atrium were so prolonged that the sinus node was never reset by the premature atrial depolarisations. Increasing prolongation of the atrial recovery cycle in the rabbit with progressively more premature atrial depolarisations has been attributed to a progressive increase of conduction time of the stimulus into the sinus node and a consequent shift of pacemaker within the sinus node (Bonke *et al.*, 1971).

The range of sinoatrial conduction time values in the 17 patients in our study was similar to that observed in other studies (Engel *et al.*, 1973; Reiffel *et al.*, 1974; Hirschfeld *et al.*, 1975; Masini *et al.*, 1975). Our conclusion that sinoatrial conduction time does not afford any distinction between patients with sinoatrial disease and those without, is in agreement with that of Hirschfeld *et al.* (1975) and differs from that of Reiffel *et al.* (1974), Masini *et al.* (1975) and Breithardt *et al.* (1976). In a more recent paper from Strauss *et al.* (1976) the indirectly measured sinoatrial conduction time was prolonged in 6 of 16 patients with sinoatrial disease.

The dependency of sinoatrial conduction time on basic sinus cycle length was first suggested by Reiffel *et al.* (1974). However, as pointed out by these authors, their method of showing the relation by calculating mean sinoatrial conduction times for groups of longer, shorter, and intermediate sinus cycles, introduces a statistical effect which will exaggerate any apparent inverse relation of sinoatrial conduction time to previous sinus cycle length. We chose to indicate the relation of sinoatrial conduction time to basic sinus cycle length by plotting all the sinoatrial conduction time values $\left(\frac{\text{RC}-\text{PC}}{2}\right)$ against previous sinus cycle length values in the plateau zone from each patient individually. The wide scatter of the calculated values of sinoatrial conduction times compared with the limited range of previous sinus cycle lengths in most patients meant that acceptable regression lines could not be fitted.

When, however, a composite SACT/PC plot was made of all the values from each of the 17 patients the inverse correlation between sinoatrial conduction time and previous sinus cycle length was poor (slope gradient RC = 0·83 PC). Correction of individual sinoatrial conduction time values for basic sinus cycle length appeared, therefore, inappropriate as it could only be based on this poor regression obtained from the composite results.

The failure to obtain a satisfactory plateau zone in a third of our patients, the uncertainty of correction for basic sinus cycle length, and the wide range of the results in our control group (Table 2) were major objections to the application of this technique to the identification of patients with sinoatrial disease.

In addition to the methodological limitations of this technique, it remains questionable whether sinoatrial conduction time measured in this way is representative of the true conduction time between the sinus node and the adjacent atrium. With direct recording from the sinus node and the surrounding atrium, conduction times of 10 to 60 ms have been recorded in the rabbit (Paes de Carvalho *et al.*, 1959; Klein *et al.*, 1973; Yamaguchi and Mandel, 1975). The properties of the sinoatrial fibres are in keeping with a conduction delay at this site (Strauss and Bigger, 1972). However, direct records have not been made in man. Any direct measurement of sinoatrial conduction time would depend on the exact sites of the recording electrodes and such measurements may not relate to the physiological value obtained by the indirect method of measuring sinoatrial conduction time. An essential premise for the calculation of sinoatrial conduction time by the indirect method is that the return atrial cycle length is comparable to the previous sinus cycle length, plus conduction time from the atrium into the sinus node and from the sinus node back to the atrium. However, microelectrode studies in rabbits have shown that the returning sinus node cycle after a premature atrial depolarisation may be prolonged or shortened compared with the basic sinus node cycle length and that variation of retrograde and anterograde conduction between sinus node and atrium occurs in different rabbits (Klein *et al.*, 1973). The duration of the return sinus node cycle after a premature atrial depolarisation may be longer or shorter than the normal spontaneous sinus cycle length and may vary with the prematurity of the test stimulus (Bonke *et al.*, 1969, 1971). Such considerations from animal work throw doubt on the validity of the calculation of sinoatrial conduction time by the indirect method and may also explain some of the practical difficulties with the use of this technique that we have observed in man. Indirect measurements may be an overestimate if, as a result of the premature atrial depolarisations, the sinus node return cycle or conduction interval between the sinus node and the atrium has been prolonged.

At present, sinus node recovery time and the indirect measurement of sinoatrial conduction time have been the most widely used electrophysiological. techniques for the assessment of sinoatrial disease. This present study has failed to confirm that these measurements are of any clinical value.

References

Bonke, F. I. M., Bouman, L. N., and Schopman, F. J. G. (1971). Effect of an early atrial premature beat on activity of the sinoatrial node and atrial rhythm in the rabbit. *Circulation Research*, **29**, 704–715.

Bonke, F. I. M., Bouman, L. N., and van Rijn, H. E. (1969). Change of cardiac rhythm in the rabbit after an atrial premature beat. *Circulation Research*, **24**, 533–544.

Bouvrain, Y., Slama, R., and Temkine, J. (1967). Le bloc sinoauriculaire et les "maladies du sinus". *Archives des Maladies du Coeur et des Vaisseaux*, **60**, 753–773.

Breithardt, G., Siepel, L., Both, A., and Loogen, F. (1976). Calculated sino-atrial conduction time (SACT) in patients with normal and abnormal sinus node function. Abstracts of Free Communications, VII European Congress of Cardiology, Amsterdam.

Crook, B. R. M., and Cashman, P. M. M. (1976). The R-R interval histogram. *Postgraduate Medical Journal*, **52**, Suppl. 7, 46–53.

Crook, B. R. M., Cashman, P. M. M., Stott, F. D., and Raftery, E. B. (1973). Tape monitoring of the electrocardiogram in ambulant patients with sino-atrial disease. *British Heart Journal*, **35**, 1009–1013.

Engel, T. R., Bond, R. C., and Schaal, S. F. (1973). First degree sinoatrial heart block. *Circulation* **47–48**, Suppl. IV, 161.

Goldreyer, B. N., and Damato, A. N. (1971). Sinoatrial-node entrance block. *Circulation*, **44**, 789–802.

Greenwood, R. J., and Finkelstein, D. (1964). *Sinoatrial Heart Block*. (American Lecture Series). Thomas, Springfield, Illinois.

Gupta, P. K., Lichstein, E., Chadda, K. D., and Badui, E. (1974). Appraisal of sinus nodal recovery time in patients with sick sinus syndrome. *American Journal of Cardiology*, **34**, 265–270.

Hirschfeld, D. S., Peters, R., Kunkel, F., and Scheinman, M. M. (1975). Sinoatrial conduction time (SACT) and abnormal perinodal refractoriness in patients with sinus node disease (SND). *Circulation*, **51–52**, Suppl. 11, 112.

Klein, H. O., Singer, D. H., and Hoffman, B. F. (1973). Effects of atrial premature systoles on sinus rhythm in the rabbit. *Circulation Research*, **32**, 480–491.

Lee, C. H., Cohen, L. S., and Cannom, D. S. (1975). Limitations of sinoatrial recovery time in assessing sinus node dysfunction. *Circulation*, **52**, Suppl. II, 12.

Mandel, W., Hayakawa H, Danzig, R., and Marcus, H. S. (1971). Evaluation of sinoatrial node function in man by overdrive suppression. *Circulation*, **44**, 59–66.

Masini, G., Dianda, R., and Grazina, A. (1975). Analysis of sino-atrial conduction in man using premature atrial stimulation. *Cardiovascular Research*, **9**, 498–508.

Narula, O. S., Samet, P., and Javier, R. P. (1972). Significance of the sinus-node recovery time. *Circulation*, **45**, 140–158.

Paes de Carvalho, A., de Mello, W. C., and Hoffman, B. F. (1959). Electrophysiological evidence for specialised fiber types in rabbit atrium. *American Journal of Physiology*, **196**, 483–488.

Reiffel, J. A., Bigger, J. T., and Konstam, M. A. (1974). The relationship between sinoatrial conduction time and sinus cycle length during spontaneous sinus arrhythmia in adults. *Circulation,* **50,** 924–934.

Strauss, H. C., and Bigger, J. T. (1972). Electrophysiological properties of the rabbit sinoatrial perinodal fibres. *Circulation Research,* **31,** 490–506.

Strauss, H. C., Bigger, J. T., Saroff, A. L., and Giardina, E. G. V. (1976). Electrophysiologic evaluation of sinus node function in patients with sinus node dysfunction. *Circulation,* **53,** 763–776.

Strauss, H. C., Saroff, A. L., Bigger, J. T., and Giardina, E. G. V. (1973). Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man. *Circulation,* **47,** 86–93.

Yamaguchi, I., and Mandel, W. (1975). Effects of antiarrhythmic drugs on sinus node to atrial conduction time in isolated atrial tissue. *Circulation,* **51–52,** Suppl. II, 259.

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Pathological studies in sinoatrial disorder (sick sinus syndrome)

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Necropsy data from a series of 8 patients diagnosed during life as having chronic sinoatrial disorder (sick sinus syndrome) are presented. The morphology of the cardiac conducting system was studied by serial section, and the coronary vasculature was examined in detail in 5 of the 8 patients by the injection of a radiopaque medium, and in all 8 by routine histological methods. The sinoatrial nodes were found to be abnormal in 7 of the 8 patients. In 4 the node was atrophic, in 3 there was a pronounced increase in the amount of fibrous tissue present in the node, and in only one case did the node appear normal on light microscopy. In 1 of the 3 patients with fibrosed nodes amyloid tissue was found in the node itself, and heavy deposition was noted in the atrial musculature surrounding the node. The sinoatrial-node artery was patent in all cases and major narrowing of the larger coronary arteries was found in only 1 case. Histological abnormalities were found in the atrioventricular conducting tissue in all but 1 case, changes being seen either in the atrioventricular node or in the His-Purkinje system. It is concluded that the aetiology of sinoatrial disease is multifactorial, but that at least in the cases studied coronary arteriosclerosis was not responsible.

Since the description by Short (1954) of a syndrome of alternating bradycardia and tachycardia, there has been a growing volume of published reports on what has become known as sinoatrial disorder (Lloyd-Mostyn *et al.*, 1973). There have been papers from several countries describing its various clinical features, and modes of presentation, under such synonyms as sick sinus or lazy sinus syndrome (Bouvrain *et al.*, 1967; Ferrer, 1968; Shaw and Eraut, 1969). Furthermore, the treatment of the condition using both electrical and pharmacological methods and its mortality and morbidity have been described (Eraut and Shaw, 1971; Aroesty *et al.*, 1974), and a complete monograph on the subject has recently been published (Ferrer, 1974).

There have been, however, very few reports of necropsy studies; indeed, a review of the published material produced only 11 cases of sinoatrial disorder of a chronic nature, in which some specialised examination of the conduction system had been undertaken at necropsy (Rossi, 1969; Patton *et al.*, 1970; Rasmussen, 1971; Rosen *et al.*, 1971; Rubinstein *et al.*, 1972; Kaplan *et al.*, 1973; Kulbertus *et al.*, 1973; Warembourg *et al.*, 1974; Sauerwein *et al.*, 1976). Of these, the morphology of the sinoatrial node, atrial musculature, and the other parts of the specialised conducting system of the heart, together with its vascular supply were adequately described in only 7 (Rosen *et al.*, 1971; Kaplan *et al.*, 1973; Kulbertus *et al.*, 1973; Warembourg *et al.*, 1974; Sauerwein *et al.*, 1976).

The study described here was undertaken to investigate the morphological changes associated with sinoatrial disorder. Since arteriosclerosis was a common finding in the cases previously reported, a particular attempt was made to study the vascular supply to the sinoatrial node and lower part of the conducting system.

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Subjects and methods

Material for the study was obtained from patients dying while in the Devon Heart Block and Bradycardia Survey (Shaw and Eraut, 1970). Patients were considered to have sinoatrial disorder if the electrocardiogram showed sinus bradycardia with one or more of the following associated arrhythmias.

(1) Periods of sinus arrest or sinoatrial block in which cessation of atrial activity persisted for 2 seconds or longer.

(2) Profound atrial slowing (below 40 per minute with or without a supervening junctional rhythm).

(3) Fast atrial arrhythmias, namely atrial fibrilla-

tion, atrial flutter, or paroxysmal atrial tachycardia.

For the purposes of this study sinus bradycardia was defined as a chronic sinus rate below 50 per minute in the absence of myxoedema, raised intracranial tension, jaundice, or myocardial infarction, or myopericarditis within the preceding 28 days.

Hearts from 8 patients fulfilling these criteria subsequently became available at necropsy. All patients had had electrocardiographically documented bradycardia, with a heart rate below 40 beats per minute, and all patients in whom a more extensive investigation was possible had shown such features as sinus arrest or supraventricular tachycardia. Conduction disturbances had also been shown in 4 of the 8 patients; these ranged from right bundle-branch block to complete heart block. Average follow-up time for the patients was 3 years and permanent pacemakers had been used in 2 (see Tables 1 and 2).

Necropsies were carried out as soon as possible after death, and the heart was removed complete, care being taken to retain 2 to 3 cm of the proximal portion of the superior vena cava, in order to obtain the sinoatrial node intact. Furthermore, this method avoided damage to the coronary arteries so that post-mortem angiography could be undertaken. Five of the 8 cases were suitable for perfusion, and in these the coronary vasculature was injected with a radiopaque medium. Originally a barium-gelatin mixture was used; latterly, however, the coloured barium suspension, Colorpaque, was used, and this is now felt to be the method of choice (Farrer-Brown, 1968), since the material consistently penetrated into vessels of a diameter of between 25 and 30 mμm. The vessels were perfused with the mixture at a pressure of 130 mmHg for 10 minutes. After injection, the hearts were *x*-rayed on fine grain industrial film (Industrex-D Kodak) using an Elema-Schonander skull unit; in addition, in 2 cases use was made of the xero-radiography process, plates being taken on a Sennengraph machine of the type used for mammography.

A block of tissue containing the sinoatrial node was then removed, and pinned out flat. This block included the whole of the superior vena caval ring, the crest of the right atrium, the sinoatrial node and its immediate approaches, and part of the roof of the right atrium. This portion was then re-*x*-rayed in order to show the vasculature in the area of the sinoatrial node. The heart was fixed for 2 to 3 weeks, and then blocks were taken for histological examination. During this process the interventricular septum was dissected free of the walls of the ventricles and re-*x*-rayed to examine the vascular supply to the atrioventricular node and bundle of His.

Some 30 to 40 blocks of tissue were taken, including representative portions of both atria, the interatrial septum, the coronary arteries, the sinoatrial-node artery, the approaches to the sinoatrial node, the atrioventricular node, the main bundle, and the bundle-branches, the right and left ven-

Table 2 *Atrial rate and rhythm and conduction disturbances recorded*

Case No.	*Arrhythmia*	*Slowest atrial rate*	*Conduction disturbance*
4	SB, SA, JEB, JR, A fib, WP	28	None
5	SB, JEB, JR, A fl, SA, A fib	25	1st degree AV block
11	SB	35	RBBB, CHB
17	SB, JR	33	None
35	SB, AT	39	None
36	SB, AT, A fib	24	1st degree AV block
37	SB	35	None
39	SB, SA	39	RBBB, 1st degree AV block

SB, sinus bradycardia; SA, sinus arrest; JEB, junctional escape beats; JR, junctional rhythm; A fib, atrial fibrillation; WP, wandering pacemaker; A fl, atrial flutter; AT atrial tachycardia; RBBB, right bundle-branch block; CHB, complete heart block.

Table 1 *Clinical details*

Case No.	*Age (y)*	*Follow-up time (m)*	*Clinical features*	*Paced/non-paced*	*Cause of death*
4	65	58	Adams-Stokes attacks; dizzy attacks; dyspnoea; peripheral oedema	Paced	Pacemaker failure
5	75	6	Adams-Stokes attacks; dizzy attacks	Non-paced	Cerebral thrombosis
11	93	3	Dementia	Non-paced	Congestive cardiac failure
17	69	41	Dyspnoea	Non-paced	Gram-negative septicaemia
35	69	58	Angina; dyspnoea	Non-paced	Myocardial infarction
36	64	89	Adams-Stokes attacks; dizzy attacks; palpitations, dyspnoea; angina; peripheral oedema	Paced	Left ventricular failure
37	45	21	Down's syndrome; Adams-Stokes attacks	Non-paced	Tuberculosis
39	88	12	Dizzy attacks	Non-paced	Bronchopneumonia

tricles, and the interventricular septum. The method used was a modification of that described by Davies (1967).

The blocks which contained the sinoatrial node were sectioned at a thickness of 6 μm, every 10th section was stained for study, and every 5th kept in reserve. A similar procedure was followed with the atrioventricular node and bundle and bundle-branches. Representative sections were taken from all of the other blocks for study.

The tissue was stained with either haemotoxylin and eosin, Verhoeff, van Gieson, or the Lendrum modification of the trichrome stain. Sections from all cases were also stained with Alcin blue (Lendrum *et al.*, 1972) in an attempt to show any infiltration with amyloid material. The angiographic plates were compared with 50 other angiograms performed on patients without evidence of sinoatrial disorder, and histology was compared with the sections obtained from 40 patients who had normal sinoatrial function before death.

Results

VASCULATURE

In 1 of the 8 cases (case 35) the angiograms indicated a poorly preserved vasculature, with all 3 major vessels being severely narrowed, particularly those on the left side, which were almost completely blocked in several areas. These findings were confirmed on later microscopy. In 1 further case (case 11) angiography showed mild to moderate narrowing of the major vasculature, the anterior descending branch of the left coronary being most seriously affected. Histological studies confirmed the narrowing to be the result of atheromatous deposit. In the remaining 6 cases the main coronary vessels showed surprisingly little atheroma (Fig. 1). In all the cases in which angiography was possible (5 of the 8), the artery to the sinoatrial node was well seen (Fig. 2), even in the 2 cases (cases 11 and 35) where there was atheromatous narrowing of the major vasculature.

The artery to the sinoatrial node was found to be patent in all 8 cases. It originated from the right coronary artery in 6 subjects, and from the circumflex branch of the left coronary artery in the remaining 2. On microscopy the artery was normal in 6 of the cases, and showed mild medial hypertrophy in the remaining 2 cases. The artery to the atrioventricular node and main bundle was patent in all 8 cases (Fig. 3), and in every instance the posterior descending artery which gave rise to the vessel was a branch of the right coronary. In 6 subjects the artery was normal, and in the remaining 2 showed mild medial hypertrophy.

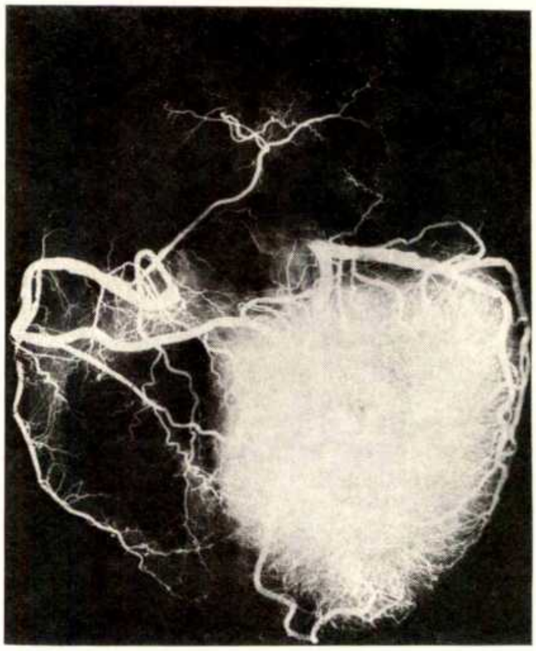

Fig. 1 *Post-mortem coronary angiogram (case 36). The artery supplying blood to the atria and sinoatrial node originates from the right coronary within 2 to 3 cm of its origin and runs upwards towards the centre of the upper third of the frame.*

MORPHOLOGY OF CONDUCTING TISSUE

Sinoatrial node

The normal sinus node consists of a discrete meshwork of fibrous tissue surrounding a central artery. The specialised muscle (or pacemaker) cells are intertwined in the fibrous tissue (Fig. 4), and usually make up between 40 and 50 per cent of the nodal surface area as determined by point counting techniques (Davies and Pomerance, 1972).

In 7 of the 8 patients described in this series the sinus node was significantly abnormal. In 4 cases (cases 4, 36, 37, and 39) the nodes were very small (Fig. 5 and 6), and are described as atrophic in Table 3, which summarises the histological findings. The normal sinoatrial node, with the usual ratio of muscle to fibrous tissue shown in Fig. 4, can be directly compared with the atrophic node in Fig. 5 (case 4), which is illustrated at the same magnification (×50). The bulk of the node can be seen to be reduced. This is even more obvious in Fig. 6 (case 36), where the magnification is twice that of the normal node as illustrated in Fig. 4, and yet nodal tissue makes up only a very small proportion of the frame. In 2 cases (cases 36 and 39) the

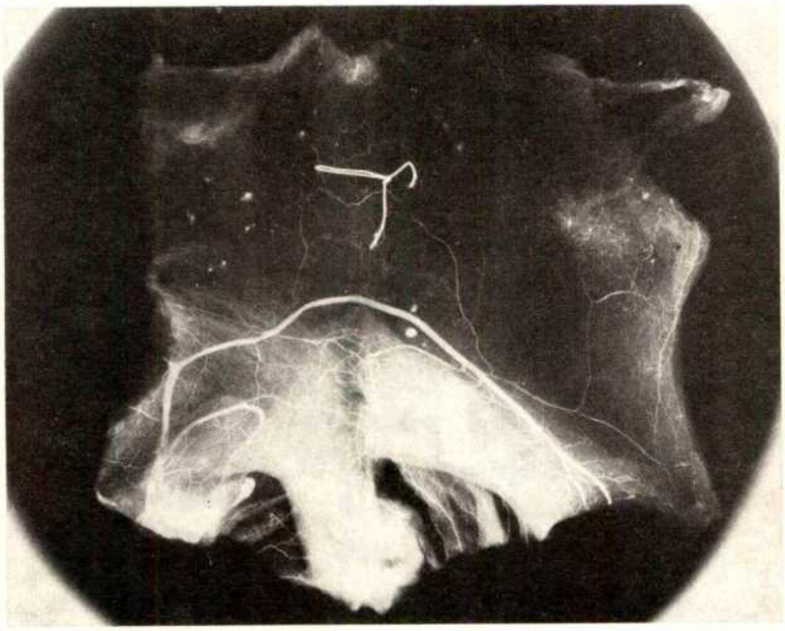

Fig. 2 *Detailed view of the sinoatrial node artery seen in Fig. 1 (case 36). The upper margin of the block consists of the superior vena cava opened out and laid flat. The lower margin is made up of the wall of the right atrial appendage. The artery to the sinoatrial node can be seen curving across the block. The node would be expected to lie more or less in the centre of the frame, around the artery, below the metallic marking tie.*

atrophic nodes were completely surrounded by adipose tissue which appeared to cut them off from the atrial myocardium on the sinoatrial node approaches.

Three patients (cases 11, 17, and 35) had nodes which were normal in size, but had very few specialised muscle fibres (less than 10% on point counting). A representative section from one of these nodes is shown in Fig. 7, taken at the same magnification as the normal node in Fig 4; there is little muscle tissue, which appears stained black, compared with the amount seen in the normal node (Fig. 4), but there is no reduction in the over-all size of the node, presumably because of a concomitant increase in the amount of fibrous tissue. In case 11 deposits of amyloid tissue were seen in the node, in addition to fibrous replacement of the node.

In 1 patient (case 5), the sinus node was normal in histological appearances.

Atrial musculature

The atrial musculature of the sinoatrial-node approaches, interatrial septum, and atria in general, including the areas where the so-called intra-atrial and internodal tracts would be expected to run, showed mild to moderate changes in 7 of the 8 cases. These consisted of mild fibrosis or slight fatty infiltration, and in 1 of these 7 cases there was a very slight deposition of amyloid material. In the 8th case there was heavy infiltration throughout the atrium with amyloid material, the muscle of the interatrial septum being completely replaced by this substance.

Atrioventricular node and bundle

The atrioventricular node and main bundle in 4 of the cases showed only minor changes, with some atrophy, slight fibrosis, and occasional mild fatty infiltration. In the remaining 4 cases, which were the ones who had conduction disturbances recorded in life, the changes were generally more widespread and severe. In cases 5 and 36 there was a moderate amount of fibrous replacement of the main bundle, particularly as it reached the summit of the interventricular septum before dividing into the right bundle-branch and the fascicles of the left bundle. In case 11 the changes were much more severe; there was a very atrophic atrioventricular node, with pronounced fibrosis, complete replacement of the main bundle by fibrous tissue, and occasional amyloid deposits throughout the conducting system. Sections from case 39 showed a small atrioventricular node with pronounced fibrosis. Fibrosis was also present in the main bundle, and there was complete replacement of muscle by fibrous tissue in the right bundle-branch.

Discussion

Acute disturbance of sinus node function is relatively common immediately after myocardial in-

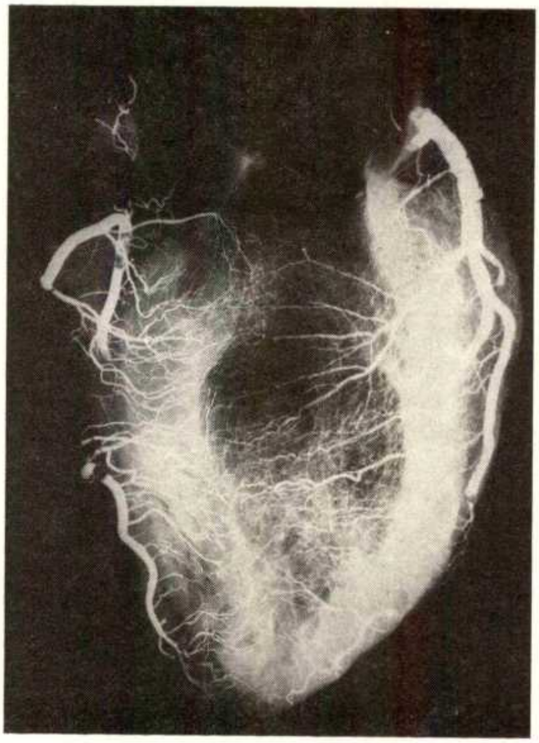

Fig. 3 *X-ray film of interventricular septum of heart (case 36) showing the artery to the atrioventricular node.*

On the left of the picture, the posterior descending artery runs vertically down the back of the interventricular septum, and on the right the anterior descending artery corresponds with it, running down the front of the interventricular septum.

The septum is well vascularised and the artery to the atrioventricular node can be seen originating from the posterior descending artery, just before that vessel makes an acute bend.

farction (James, 1968; Rokseth and Hatle, 1971), and sinus-node arterial thrombosis has been reported in patients dying soon after the event (James, 1961; Lippestad and Marton, 1967). Normal function usually returns within a few days (Fluck *et al.*, 1967), though authors reporting long-term follow-up of patients after infarction draw conflicting conclusions (Hatle *et al.*, 1976; Parameswaran *et al.*, 1976). Similarly the incidence of a past history of a myocardial infarct differs between series of cases with chronic sinoatrial disorder (Conde *et al.*, 1973; Härtel and Tarvensaari, 1975; Shaw, 1976). In the few previous necropsy descriptions of patients dying with chronic sinoatrial disorder, several authors found arteriosclerosis of the coronary vasculature and thereby imply that ischaemia is the cause of the disturbance of sinus node and atrial function (Rosen *et al.*, 1971; Kaplan *et al.*, 1973; Kulbertus *et al.*, 1973; Aroesty *et al.*, 1974), but detailed investigations of the nodal blood supply had not been made, nor had post-mortem coronary angiography been performed.

In the present study the major vessels were free from gross atheroma in all but one case, and in this instance (case 35) the sinoatrial node artery filled well with contrast media on *post-mortem* angiography. Of course it must be accepted that this technique cannot reproduce the precise conditions occurring *ante mortem*. Nevertheless, the error with this procedure tends to be a failure to fill vessels that are perfused during life, so that it would not be expected that contrast media would penetrate a previously unperfused vessel. It seems, therefore, that disease of the major coronary arteries or of the sinoatrial node artery was not responsible for the sinoatrial disorder observed in our cases. Many causes, other than disturbed blood supply, have been suggested by previous authors.

(1) Enzymatic abnormalities of the pacemaker cells such as a disturbance of cholinesterase metabolism.
(2) Infiltration of the sinoatrial node and/or its approaches, by amyloid or metastatic carcinoma.
(3) Neural factors such as abnormal vagal tone, or infiltration of the sympathetic plexus by tumour or intraneural plexus abnormalities.
(4) Idiopathic degeneration involving loss of specialised pacemaking cells in the sinus node.
(5) Fibrosis, possibly caused by past infections or an autoimmune process.
(6) Congenital abnormalities of the sinus node.

Dighton (1974) has suggested that there may be a deficiency of the enzyme cholinesterase in the autonomic nerve fibres in the sinoatrial node. Unfortunately, this hypothesis is difficult to verify with currently available techniques on material which is often 24 to 48 hours old when removed at necropsy. Such an abnormality would not be detectable on light microscopy but would be a possible explanation for the nodal dysfunction seen in the case with apparently normal sinus node structure in this series (case 5). Infiltration with amyloid may well be a cause of sinoatrial disorder in a few cases. Indeed, Kaplan *et al.* (1973) report a case in which amyloid tissue was found in the atrium and interatrial septum of a case with sinoatrial disorder, where amyloid itself was not found in the conducting system. In 1 case in this series (case 11) amyloid was found in the atria, the ventricles, and the conducting tissue system, and in a further case, amyloid appeared to be an incidental finding.

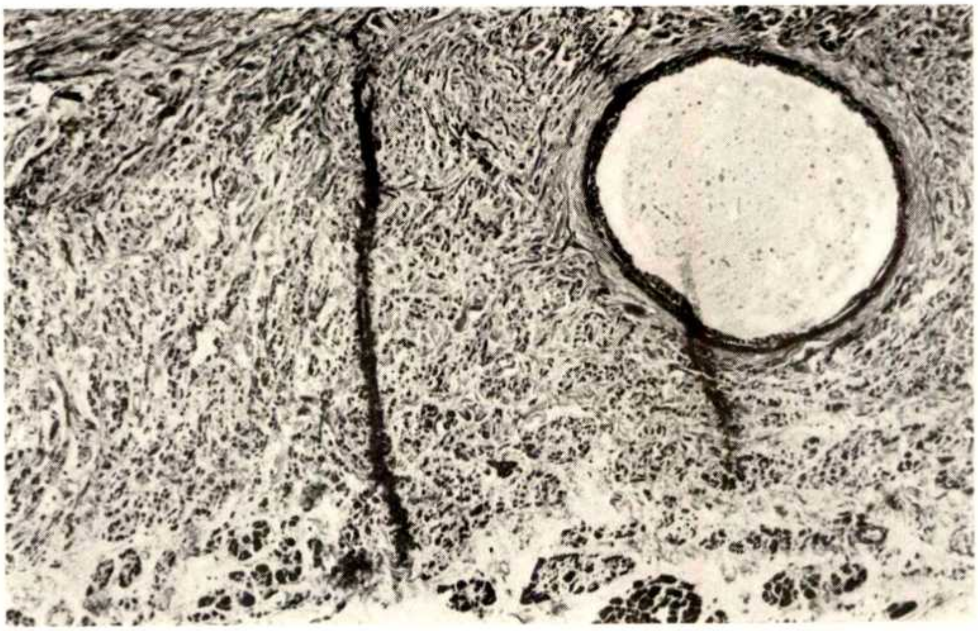

Fig. 4 *Normal sinoatrial node. (Lendrum trichrome. ×50.) Virtually the whole area of the figure is taken up by the sinoatrial node in which muscle tissue appears to be stained black. The sinoatrial node artery is in the right corner of the section and a fringe of atrial muscle appears along the bottom.*

Pearson (1945) reported a case of sinus bradycardia with cardiac asystole, and in a later paper (1950), described the *post-mortem* finding of infiltration of the mediastinum by an oat-cell bronchial carcinoma involving many of the major nerve trunks. Morphological changes in the neurones around the sinoatrial node have been described in one case (Rossi, 1969), and though it is reasonable to assume that such abnormalities may affect cardiac rhythm, no evidence was available from the cases examined in this study to confirm a neural aetiology of sinoatrial disorder.

The principal findings in 7 of the 8 cases described here were of atrophy or heavy fibrosis in the sinoatrial node. It was suggested by Fowler *et al.* (1969) that the pathology of sinoatrial node disorder might be comparable with that found in idiopathic heart block and indeed atrophy and fibrosis do occur in the latter condition. Furthermore, the changes detected in this series were not limited to

Table 3 *Summary of pathological findings of 8 cases studied*

Case No.	*Sinoatrial node*	*Atrial musculature*	*Atrioventricular node*	*Main bundle*	*Bundle-branches*
4	Atrophic	Mild fibrosis, slight amyloidosis	Mild fibrosis	Normal	Mild fibrosis peripherally
5	Normal	Mild fibrosis	Normal	Mild fibrosis	Heavy fibrosis in bundle-branches peripherally
11	Moderate fibrosis, amyloid deposits	Almost total replacement with amyloid	Atrophy, heavy fibrosis, fatty infiltration	Practically total fibrosis, some amyloid deposits	Heavy fibrosis
17	Heavy fibrosis	Mild fibrosis	Normal	Normal	Normal
35	Heavy fibrosis	Mild fatty infiltration	Mild fibrosis, slight fatty infiltration	Normal	Mild fibrosis in bundle-branches
36	Atrophic and surrounded by adipose tissue	Mild fibrosis	Some atrophy, slight fatty infiltration, mild fibrosis	Moderate fibrosis, mild fatty infiltration	Some atrophy
37	Atrophic, mild fibrosis	Fatty infiltration	Somewhat atrophic—some fatty infiltration	Mild fatty infiltration	Normal
39	Atrophic and surrounded by adipose tissue	Fatty infiltration, mild fibrosis	Heavy fibrosis, fatty infiltration	Heavy fibrosis	RBB completely fibrosed, LBB moderate fibrosis

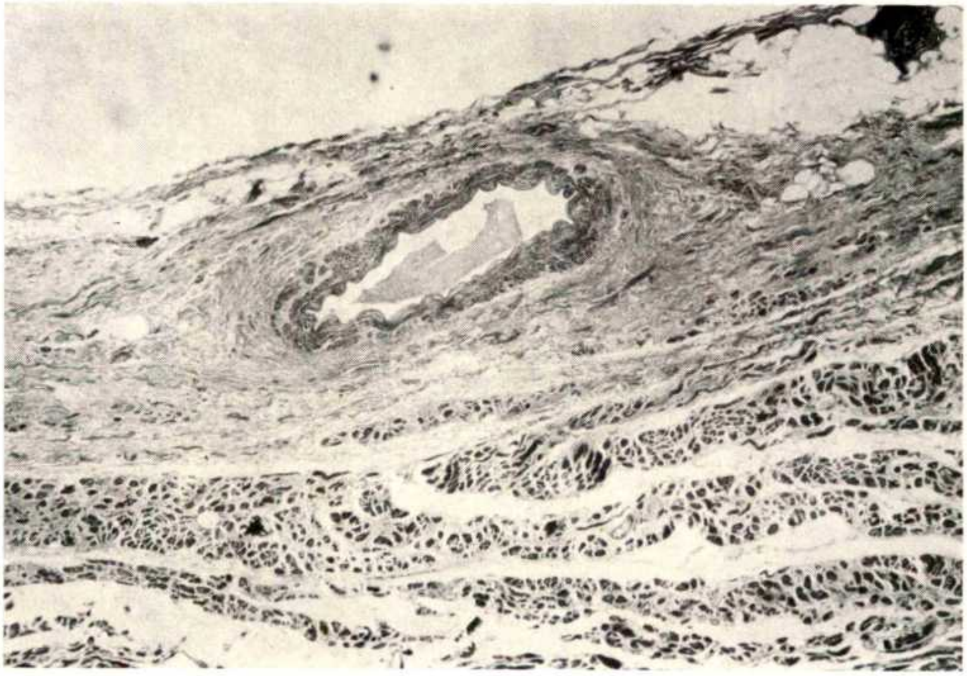

Fig. 5 *Sinoatrial node (case 4). (Lendrum trichrome. ×42.) An atrophic and fibrosed node distributed around a central artery.*

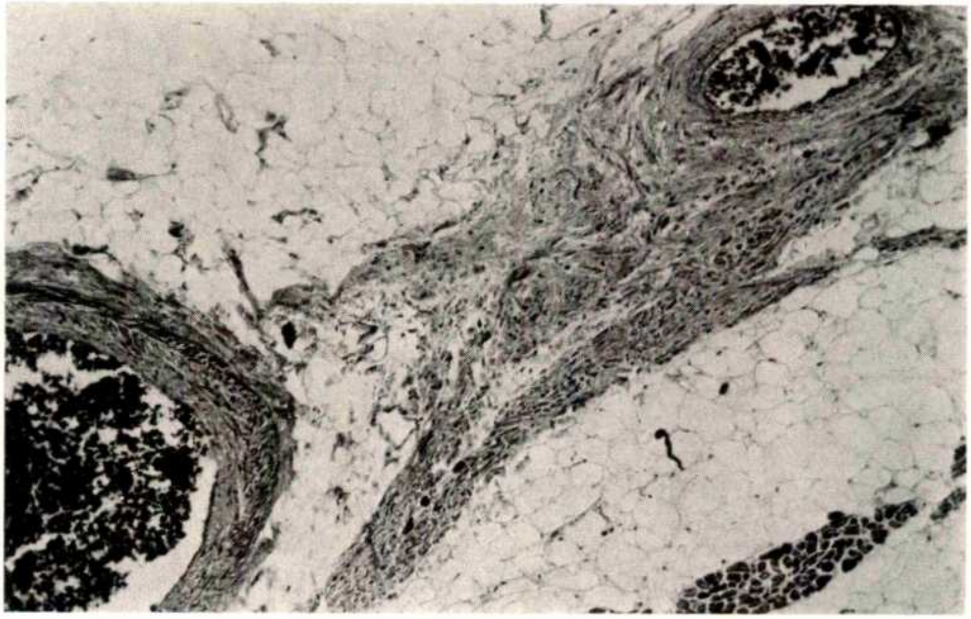

Fig. 6 *Sinoatrial node (case 36). (Lendrum trichrome. ×84.) Grossly atrophic node. The sinoatrial-node artery, which contains injectate, has split into 2 branches. What nodal tissue is present lies between the arteries completely surrounded by fat. This is the best preserved portion of a node which was much reduced in size, and also contains very little muscle tissue.*

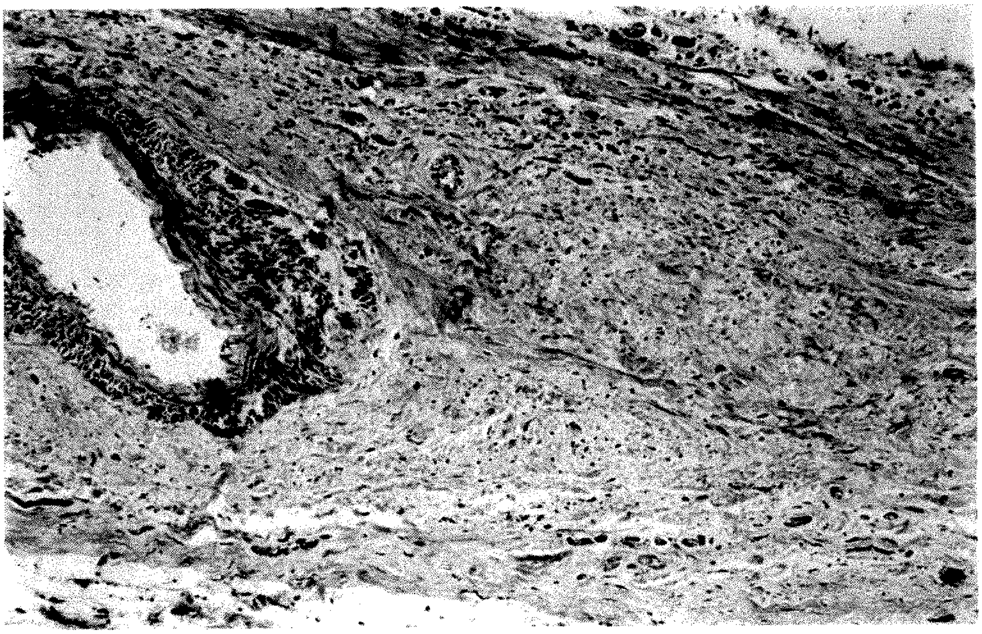

Fig. 7 *Sinoatrial node (case 35). (Lendrum trichrome. ×42.) The artery is to the left of the illustration. There is heavy replacement fibrosis of the node as shown by the paucity of muscle tissue, which appears to be stained black, compared with the normal node (Fig. 4). No reduction in the overall bulk of the node.*

the sinoatrial node, but also involved the atrial musculature, the sinoatrial node approaches, the interatrial septum, where the so-called internodal tracts would be expected to run, and the distal portion of the conducting system. The fibrosis seen in the sinoatrial node and sinoatrial node approaches could be the end result of one of a number of previous pathological conditions. Infective and inflammatory diseases, such as diphtheria, rheumatic fever, or viral pericarditis, might be followed by damage and replacement fibrosis, and have been blamed by some authors for causing sinoatrial disorder (Rasmussen, 1971; Rokseth and Hatle, 1971; Ferrer, 1973). Autoimmunological mechanisms have been suggested for the fibrosis and degeneration seen in heart block (Fairfax and Leatham, 1975), and similar mechanisms might apply in sinoatrial disorder. Certainly the results presented here should not be interpreted in such a way as to rule out the possibility of small blood vessel disease since the methods used were not capable of allowing accurate assessment of vessels smaller than 30 μm.

The hypothesis that sinoatrial disorder may have a congenital or familial basis is supported by papers by Williams *et al.* (1972) and Caralis and Varghese (1976). The former authors described 3 of 5 children in a family who had episodes of persistent atrial standstill, but histological studies are not available.

It appears that sinoatrial disorder may be produced by a variety of conditions and could, therefore, be considered comparable to chronic atrioventricular block. In case 5, where the sinoatrial node was normal to light microscopy, an ultrastructural or cholinesterase production defect could not be ruled out. Loss or replacement of pacemaker tissue was, however, the usual finding, without significant coronary artery disease. Where the outline of the sinus node appears very reduced in size (atrophy) a congenital aplasia or hypoplasia could be postulated. In contrast, when nodal size is normal but specialised muscle tissue is replaced by fibrous tissue (fibrosis), an acquired disease, perhaps myocarditic or autoimmune, can be postulated, while further information is required concerning the smaller blood vessels. Age-related loss of specialised nodal fibres, which is almost universal, would potentiate either nodal hypoplasia or fibrosis.

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References

Aroesty, J. M., Cohen, S. I., and Morkin, E. (1974). Bradycardia-tachycardia syndrome: results in twenty-eight patients treated by combined pharmacologic therapy and pacemaker implantation. *Chest,* **66,** 257–263.

Bouvrain, Y., Slama, R., and Temkine, J. (1967). Le bloc sino-auriculaire et 'les maladies du sinus'. Réflexions à propos de 63 observations. *Archives des Maladies du Coeur et des Vaisseaux,* **60,** 753–773.

Caralis, D. G., and Varghese, P. J. (1976). Familial sinoatrial node dysfunction. Increased vagal tone a possible aetiology. *British Heart Journal,* **38,** 951–956.

Conde, C. A., Leppo, J., Lipski, J., Stimmel, B., Litwak, R., Donoso, E., and Dack, S. (1973). Effectiveness of pacemaker treatment in the bradycardia-tachycardia syndrome. *American Journal of Cardiology,* **32,** 209–213.

Davies, M. J. (1967). A histological study of the conduction system in complete heart block. *Journal of Pathology and Bacteriology,* **94,** 351–358.

Davies, M. J., and Pomerance, A. (1972). Quantitative study of ageing changes in the human sinoatrial node and internodal tracts. *British Heart Journal,* **34,** 150–152.

Dighton, D. H. (1974). Sinus bradycardia: autonomic influences and clinical assessment. *British Heart Journal,* **36,** 791–797.

Eraut, D., and Shaw, D. B. (1971). Sinus bradycardia. *British Heart Journal,* **33,** 742–749.

Fairfax, A. J., and Leatham, A. (1975). Idiopathic heart block: associated with vitiligo, thyroid disease, pernicious anaemia and diabetes mellitus. *British Medical Journal,* **4,** 322–324.

Farrer-Brown, G. (1968). The injection of capillaries, arterioles, and arteries in the ventricles of the human heart by a radio-opaque medium. *Cardiovascular Research,* **2,** 179–186.

Ferrer, M. I. (1968). The sick sinus syndrome in atrial disease. *Journal of the American Medical Association,* **206,** 645–646.

Ferrer, M. I. (1973). The sick sinus syndrome. *Circulation,* **47,** 635–641.

Ferrer, M. I. (1974). *The Sick Sinus Syndrome.* Futura, Mount Kisco, New York.

Fluck, D. C., Olsen, E., Pentecost, B. L., Thomas, M., Fillmore, S. J., Shillingford, J. P., and Mounsey, J. P. D. (1967). Natural history and clinical significance of arrhythmias after acute cardiac infarction. *British Heart Journal,* **29,** 170–189.

Fowler, P. B. S., Ikram, H., Maini, R. N., Makey, A. R., and Kirkham, J. S. (1969). Bradycardic angina: haemodynamic aspects and treatment. *British Medical Journal,* **1,** 92–94.

Härtel, G., and Tarvensaari, T. (1975). Treatment of sinoatrial syndrome with permanent cardiac pacing in 90 patients. *Acta Medica Scandinavica,* **198,** 341–347.

Hatle, L., Bathen, J., and Rokseth, R. (1976). Sino-atrial disease in acute myocardial infarction long-term prognosis. *British Heart Journal,* **38,** 410–414.

James, T. N. (1961). Myocardial infarction and atrial arrhythmias. *Circulation,* **24,** 761–776.

James, T. N. (1968). The coronary circulation and conduction system in acute myocardial infarction. *Progress in Cardiovascular Diseases,* **10,** 410–449.

Kaplan, B. M., Langendorf, R., Lev, M., and Pick, A. (1973). Tachycardia-bradycardia syndrome (so-called 'sick sinus syndrome'). *American Journal of Cardiology,* **31,** 497–508.

Kulbertus, H. E., De Leval-Rutten, F., and Demoulin, J. C. (1973). Sino-atrial disease: a report on 13 cases. *Journal of Electrocardiology,* **6,** 303–312.

Lendrum, A. C., Slidders, W., and Fraser, D. S. (1972). Renal hyalin: a study of amyloidosis and diabetic fibrinous vasculosis with new staining methods. *Journal of Clinical Pathology,* **25,** 373–396.

Lippestad, C. T., and Marton, P. F. (1967). Sinus arrest in proximal right coronary artery occlusion. *American Heart Journal,* **74,** 551–556.

Lloyd-Mostyn, R. H., Kidner, P. H., and Oram, S. (1973). Sinuatrial disorder including the brady-tachycardia syndrome: a review with addition of 11 cases. *Quarterly Journal of Medicine,* New Series, **42,** 41–57.

Parameswaran, R., Ohe, T., and Goldberg, H. (1976). Sinus node dysfunction in acute myocardial infarction. *British Heart Journal,* **38,** 93–96.

Patton, R. D., Damato, A. N., Berkowitz, W. D., Lau, S. H., and Stein, E. (1970). The electrically silent right atrium. *Journal of Electrocardiology,* **3,** 239–243.

Pearson, R. S. B. (1945). Sinus bradycardia with cardiac asystole. *British Heart Journal,* **7,** 85–90.

Pearson, R. S. B. (1950). Sinus bradycardia with cardiac asystole. *British Heart Journal,* **12,** 61–64.

Rasmussen, K. (1971). Chronic sinoatrial heart block. *American Heart Journal,* **81,** 38–47.

Rokseth, R., and Hatle, L. (1971). Sinus arrest in acute myocardial infarction. *British Heart Journal,* **33,** 639–642.

Rosen, K. M., Rahimtoola, S. H., Gunnar, R. M., and Lev, M. (1971). Transient and persistent atrial standstill with His bundle lesions: electrophysiologic and pathologic correlations. *Circulation,* **44,** 220–236.

Rossi, L. (1969). *Histopathologic Features of Cardiac Arrhythmias.* Casa Editrice Ambrosiana, Milano.

Rubenstein, J. L., Schulman, C. L., Yurchak, P. M., and Desanctis, R. W. (1972). Clinical spectrum of the sick sinus syndrome. *Circulation,* **46,** 5–13.

Sauerwein, H. P., Roos, J. C., Becker, A. E., and Dunning, A. J. (1976). The sick sinus syndrome. *Acta Medica Scandinavica,* **199,** 467–473.

Shaw, D. B. (1976). The etiology of sino-atrial disorder (sick sinus syndrome). *American Heart Journal,* **92,** 539–540.

Shaw, D. B., and Eraut, D. (1969). Atrial bradycardia or the lazy sinus syndrome. *Bristol Medico-Chirurgical Journal,* **84,** 213–215.

Shaw, D. B., and Eraut, D. (1970). Prevalence and morbidity of heart block in Devon. *British Medical Journal,* **1,** 144–147.

Short, D. S. (1954). The syndrome of alternating bradycardia and tachycardia. *British Heart Journal,* **16,** 208–214.

Warembourg, H., Théry, C., Lekieffre, J., Delbecque, H., and Gosselin, B. (1974). Blocs sino-auriculaires et blocs auriculo-ventriculaires associés. *Archives des Maladies du Coeur et des Vaisseaux,* **67,** 787–795.

Williams, D. O., Jones, E. L., Nagle, R. E., and Smith, B. S. (1972). Familial atrial cardiomyopathy with heart block. *Quarterly Journal of Medicine,* **41,** 491–508.

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Effect of Bunaphtine on right atrial repolarisation in man

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Using a bipolar suction electrode technique, right atrial monophasic action potentials were recorded in 11 patients with recurrent attacks of paroxysmal atrial tachyarrhythmia.

The right atrial monophasic action potential total duration, measured at 90 per cent level of repolarisation, in sinus rhythm, ranged between 217 and 394 ms.

N(2-diethylamine-ethyl)N(n-buthyl)-naphtamide (Bunaphtine) was administered by an intracardiac catheter at an average dosage of 1·78 mg/kg body weight in order to evaluate its effect on atrial repolarisation. Monophasic action potential recordings were performed during drug administration and thereafter every minute for an average observation period of 12·2 minutes. The drug induced a significant lengthening of atrial repolarisation (mean 18·4%) strongly correlated with a significant reduction of relative repolarisation rate of phase 3 (RRR ph3). The effect was more obvious in patients with short repolarisation and was not correlated with significant variations in heart rate. When basic cycle length was maintained constant by atrial pacing an increase in total duration of right atrial monophasic action potential was seen. Administration of the drug was followed by an appreciable reduction of inhomogeneity of repolarisation as measured from different sites in the atrium. In 2 patients conversion from atrial fibrillation to sinus rhythm occurred during drug infusion with a progressive lengthening of right atrial monophasic action potential; this suggests that the antiarrhythmic properties of Bunaphtine are related to its direct effect on repolarisation. Thus, as far as atrial tissue is concerned Bunaphtine can be considered a Class 3 antiarrhythmic drug according to the classification of Vaughan-Williams.

N (2-diethylamine-ethyl) N (n-buthyl) naphtamide (Bunaphtine)[1] is a new drug, the antiarrhythmic properties of which have been reported as being superior to those of quinidine (Beani, 1972), while circulatory side effects appear to be less; it does not significantly affect mean arterial pressure or coronary flow. In therapeutic doses it seems to be strictly cardioactive; only at toxic levels does it induce depression of the central nervous system (Beani, 1972).

Wide clinical use has proved the effectiveness of Bunaphtine in the treatment of both ventricular and supraventricular arrhythmias, either chronic or paroxysmal (Botti, 1972; Lotto and Lomanto, 1972; Masini *et al.*, 1972; Franchini *et al.*, 1974; Vegis, 1975). Good results have been obtained also in prophylactic and therapeutic use in patients with acute myocardial infarction (Botti *et al.*, 1976).

Electrophysiological properties of Bunaphtine have been studied *in vitro* on guinea-pig and rabbit heart preparations by the microelectrode technique (Ferroni and Monticelli, 1973). The primary effects of the drug on action potentials of atrial myocardial cells are a reduction or disappearance of prepotentials, a prolongation of action potential duration, a significant reduction in heart rate, and an increase in amplitude of the action potential (Ferroni and Monticelli, 1973).

Electrophysiological studies in patients, carried out by His bundle electrogram and pacing techniques, have given some information on the effects of Bunaphtine on atrioventricular conduction (Scibilia *et al.*, 1973; Grazi *et al.*, 1974), but so far little information is available about its effect on myocardial refractory periods (Grazi *et al.*, 1975).

The monophasic action potential recording technique using a suction electrode permits a good evaluation of the action potential duration and of the course of repolarisation (Hoffman *et al.*, 1959; Shabetai *et al.*, 1968; Olsson, 1971). While it cannot

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give reliable information about the depolarisation phase, it provides an exact measure of myocardial refractoriness and of rapid changes of this (Olsson, 1971). For this reason the monophasic action potential recording technique has been recommended for the accurate study of the electrophysiology of the arrhythmias and of the mechanisms of action of antiarrhythmic drugs in clinical practice (Gavrilescu and Cotoi, 1972; Olsson, 1972; Cabasson *et al.,* 1975; Fenici *et al.,* 1975). In previous observations (Fenici *et al.,* 1974a, b) Bunaphtine was found to delay repolarisation of human atrial myocardial fibres. The present study was carried out in order to evaluate the effect of Bunaphtine on right atrial monophasic action potential in patients with recurrent paroxysmal supraventricular tachyarrhythmias, in the hope of providing a more rational basis for the clinical use of the drug.

Patients and methods

Eleven patients, 6 women and 5 men, all complaining of episodes of paroxysmal atrial tachyarrhythmia, were investigated, after informed consent had been obtained, during routine electrophysiological studies or diagnostic right heart catheterisation. In all cases except one (case 1) previous cardioactive treatment, if being given, had been discontinued at least 3 days before the procedure. All the patients, except case 1, were in sinus rhythm at the beginning of the investigation. Selected clinical data from the patients are presented in Table 1.

Right atrial monophasic action potential recordings were performed using a 7F gauge bipolar electrode catheter (USCI No 5623) modified to produce a suction electrode catheter as described in more detail elsewhere (Fenici *et al.,* 1973). Absolute electrical safety of the patient was provided. Deriving a unipolar signal using a peripheral electrode, an intracardiac electrogram was obtained along with the monophasic action potential from the same recording site; this is useful for a correct evaluation of the quality of the monophasic action potential and of the level at which recording is accomplished (Olsson, 1971). For signal amplification HP 8811A bioelectrical amplifiers were used. Recordings were performed, together with continuous oscilloscopic monitoring, directly onto a magnetic tape recorder (HP 3960M), allowing easy data storage and playback in a time expanded or compressed mode, to improve data manipulation. Tracings were transferred onto photographic paper at 100 and 200 mm/s paper speed. Suction applied was mainly 350 mmHg; it was discontinued every 2 minutes to avoid the danger of irreversible myocardial lesions (Olsson, 1971). All patients tolerated the procedure without any subjective discomfort or objective complication.

After a stable monophasic action potential recording had been obtained in basal conditions, an average dose of 1·78 mg/kg body weight of Bunaphtine was delivered, directly in the right atrium, over 1 to 2 minutes. Right atrial monophasic action potential was recorded continuously from the same site during drug administration and

Table 1 *Selected data from patients*

Case No.	*Age (y)*	*Sex*	*Diagnosis*	*Electrocardiogram*	*Paroxysmal arrhythmias*	*K (mmol/l)*	*Drugs*	*Discontinued before study*
1	44	F	MS (operated); DC shock conversion of AF with frequent relapse	SR-RAO-RVO	AFl-AF	Normal	Digitalis propranolol, quinidine	3 days ND ND
2	38	F	Thyroid adenoma	SR-N	PAT	Normal	Propranolol	10 days
3	49	F	Palpitation	SR-N	PAF	Normal	None	—
4	46	F	ASD (foramen ovale); hypothyroidism, hiatus hernia	SR-N	PAT	3·2	None	—
5	66	M	Syncopal attacks; cholelithiasis	SR-AR with CSM	PAF	Normal	Atropine	3 days
6	40	F	Cholelithiasis (operated); duodenal ulcer	SR-ant. lat. ischaemia	PAT	Normal	None	—
7	25	M	Dizziness; hiatus hernia; hypertension	SR-LVH	PAF	Normal	None	—
8	50	M	Goitre (colloid-cystic adenoma-operated)	SR-PVC	PAF	Normal	Digitalis, propranolol, quinidine	3 days
9	50	F	MS; nephrovascular hypertension	SR-LAO	PAF	3·8	KCl, quinidine, amiodarone	10 days
10	71	M	Dizziness; palpitation	SR-PAC	PAF	Normal	None	—
11	60	M	Syncopal attacks; rheumatoid arthritis	SB-PAC	—	Normal	None	—

AF, atrial fibrillation; AFl, atrial flutter; AR, atrial arrest; ASD, atrial septal defect; CSM, carotid sinus massage; LAO, left atrial overload; LVH, left ventricular hypertrophy; MS, mitral stenosis; N, normal; PAC, premature atrial contraction; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; PVC, premature ventricular contraction; RAO, right atrial overload; RVO, right ventricular overload; SB, sinus bradycardia; SR, sinus rhythm; ND, not discontinued.

Table 2 *Individual data from right atrial monophasic action potential recordings before and after Bunaphtine administration*

Case No.	*Rhythm*	*Dose (mg/kg body weight*	*Before Bunaphtine*			*After Bunaphtine*			*RA MAP dur.*		*Cycle length*
			RA MAP dur. (ms)	*Cycle length (ms)*	*RRR ph3 (%/s)*	*RA MAP dur. (ms)*	*Cycle length (ms)*	*RRR ph3 (%/s)*	*Incr. (%)*	*VC (%)*	*VC (%)*
1	A. Fl	0·81	137·8 ±16·24	254 ±8·22	309·12 ±39·5	257·4 ±14·89	336·2 ±4·8	157·57 ±19·21	86·79	42·8	19·7
2	SR	2	217·43 ±4·12	521 ±6·08	615·4 ±25·77	286 ±6·52	596 ±11·4	380·29 ±29·25	31·54	19	9·5
3	SR	1·3	233·6 ±4·16	764 ±23·29	384·16 ±12·4	311 ±3·08	680 ±14·26	259·15 ±9·25	33·13	20·1	8·28
4	SR	1·5	245·6 ±7·44	614·4 ±5·18	518·31 ±50·82	330·8 ±3·11	624·6 ±12·66	285·49 ±11·29	34·69	20·9	1·16
5	SR	2	261 ±7·71	577 ±2·74	478·52 ±12·81	305·2 ±10·76	592 ±2·74	417·75 ±5·06	16·98	11·04	1·81
6	SR	2	286·6 ±5·94	815·2 ±14·2	432·46 ±5·35	379 ±5·48	854 ±8·22	282·92 ±4·89	32·24	19·69	3·29
7	SR	1·6	292·7 ±13·65	754·6 ±54·77	406·1 ±17·46	317 ±4·36	812 ±7·85	300·14 ±12·63	8·3	5·64	5·18
8	SR	2·1	301 ±6·52	561 ±2·24	493·42 ±11·43	329 ±2·24	635 ±0	415·42 ±7·83	9·3	6·3	8·75
9	SR	1·8	325·72 ±27·49	994·5 ±45·35	303·01 ±43	334·29 ±16·73	1001·65 ±25·85	298·6 ±58·1	2·63	1·84	0·51
10	SR	1·5	354 ±8·54	917 ±9·70	306·6 ±19·23	374·4 ±9·96	929 ±6·52	279 ±6·93	5·76	3·96	0·92
11	(SR) AP 70/min	2	341·86 ±5·21	840	403·54 ±27·88	376·6 ±3·65	840 ±0	367·96 ±5·9	9·22	7·02	—
Mean values Cases 2-11		1·78 ±0·28	285·95 ±46·3	735·8 ±161·5	434·15 ±96·1	334·3 ±32·42	756·4 ±149·16	328·67 ±60·23	18·38 ± 13·02	11·55 ± 7·58	4·38 ± 3·64

AFl, atrial flutter; AP, atrial pacing; dur., duration; incr., increment; MAP, monophasic action potential; RA, right atrial; RRR ph3, relative repolarisation rate of phase 3; SR, sinus rhythm; VC, variation coefficient.

thereafter every minute for a mean observation time of 12·2 minutes.

In case 9 right atrial monophasic action potential recordings were obtained from 5 different sites in order to evaluate the degree of non-uniformity of atrial repolarisation before and after drug administration. In case 11 all the investigations were performed at a constant cycle length obtained by atrial pacing to eliminate the rate dependent variations in duration of right atrial monophasic action potential.

According to the criteria suggested by Olsson (1971) for quantitative analysis of the tracings, right atrial monophasic action potential total duration was measured at 90 per cent of the repolarisation and expressed in milliseconds (ms); preceding electric cycle length was also expressed in milliseconds. The relative repolarisation rate of phase 3 was expressed as a percentage of a second (%/s).

Statistical analysis was performed using the t test of paired differences and variation coefficients.

Results

Individual data from recordings before and after Bunaphtine administration are presented in Table 2.

PATIENTS IN SINUS RHYTHM

Before Bunaphtine the average right atrial monophasic action potential duration was 285·9±46·3 ms; the average relative repolarisation rate of phase 3 was 434·15±96·1 per cent/s, and the average cycle length was 735·77±161·9 ms. After the administration of the drug a prolongation of the average duration of right atrial monophasic action potential to 334·3±32·82 ms and of cycle length to 756·43±149·16 ms together with a reduction of relative repolarisation rate of phase 3 to 328·67±60·23 per cent/s was seen (Fig. 1).

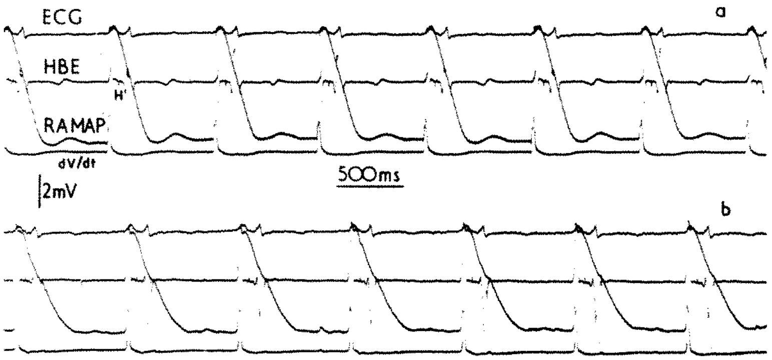

Fig. 1 *Case 6. Right atrial monophasic action potential (RA MAP) before (a) and 10 minutes after Bunaphtine (b).*

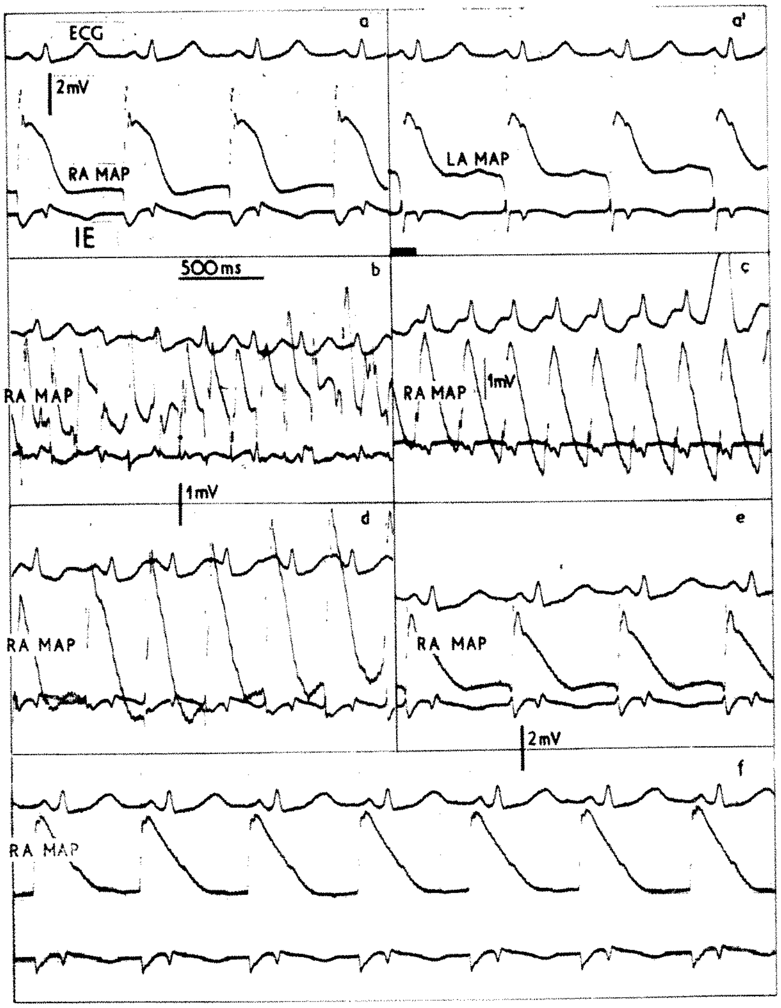

Fig. 2 *Case 4. (a-a') basic sinus rhythm (right and left atrial MAPs); (b) paroxysmal atrial fibrillation; (c) atrial flutter during drug infusion; (d) recovery of sinus rhythm (SR) (1 minute after Bunaphtine administration), (e) SR 7 minutes after Bunaphtine administration; (f) 30 minutes after Bunaphtine administration (maximum effect on RA MAP duration). IE, intracardiac electrogram.*

The average increment of right atrial monophasic action potential duration was 18·38 per cent. The average variation coefficient for monophasic action potential duration was 11·55 per cent. The largest modification of total duration of right atrial monophasic action potential was noticed at an average time of 8·1 s (range 2 to 30 s) after drug infusion.

In 2 patients (cases 4 and 10) paroxysmal atrial fibrillation occurred during the procedure and Bunaphtine was administered to regain sinus rhythm (Fig. 2 and 3). Conversion occurred in both cases with a progressive lengthening of right atrial monophasic action potential, the critical duration for the re-establishment of sinus rhythm being 195 to 210 ms. In one patient (case 4) a passage from atrial fibrillation to atrial flutter with 1:1 conduction was observed before the conversion to sinus rhythm (Fig. 2c).

In all cases a good relation between total duration of right atrial monophasic action potential and relative repolarisation rate of phase 3 variations was seen (equation for regression line $y = 844{\cdot}3 - 1{\cdot}5x$ $r = 0{\cdot}72$) (Fig. 4).

Variations of total duration of right atrial monophasic action potential and those of cycle length were poorly correlated ($y = 114{\cdot}9 + 2{\cdot}03x$; $r = 0{\cdot}61$).

Prolongation of right atrial monophasic action potential and relative repolarisation rate reduction were significant ($P < 0{\cdot}0025$), while cycle length modifications were not ($P > 0{\cdot}05$).

In case 9 the interindividual variation coefficient in basal conditions was 8·75 per cent; after Bunaph-

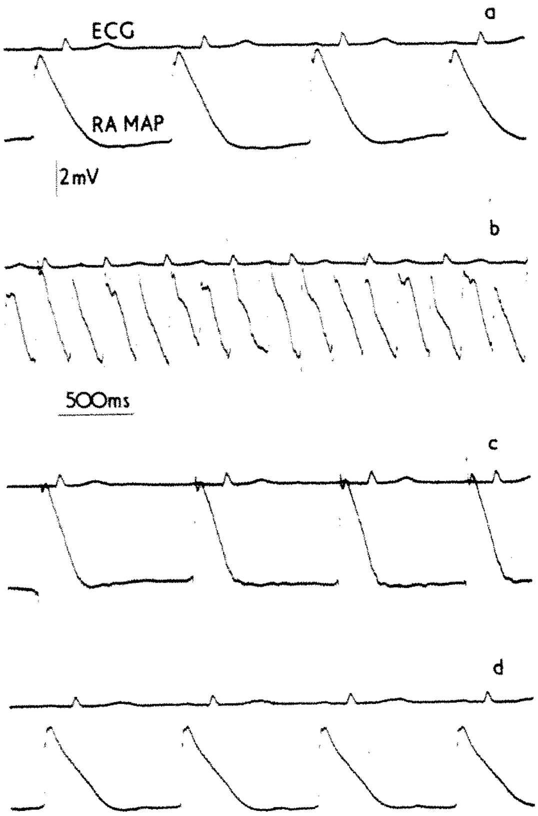

Fig. 3 *Case 10. (a) Basic sinus rhythm; (b) paroxysmal atrial fibrillation; (c) RA MAP immediately after SR re-establishment; (d) RA MAP 4 minutes after Bunaphtine administration (maximum effect on duration).*

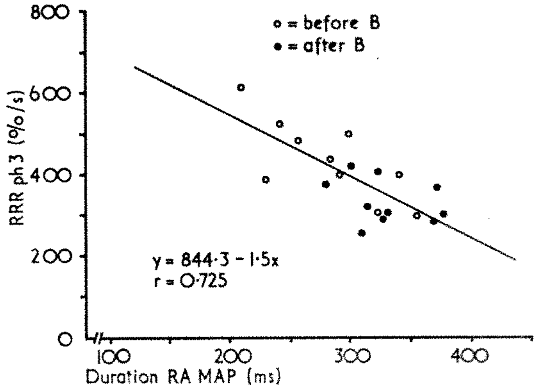

Fig. 4 *Relation between relative repolarisation rate of phase 3 (RRR ph3) and duration of right atrial MAP (RA MAP TD).*

tine administration this was reduced to 5 per cent. In this case the lowest increment in total duration of right atrial monophasic action potential was observed (2·63%). In case 11 the increment was 9·2 per cent, with a variation coefficient of 7 per cent; the interindividual variation coefficient before drug administration was 4·19 per cent.

PATIENT IN ATRIAL FLUTTER (FIG. 5)

(This case was not included in the statistical evaluation because previous cardioactive treatment had not been withdrawn and could have distorted the results.)

Basal right atrial monophasic action potential total duration was 137·8 ms; after Bunaphtine prolongation up to 257·4 ms was observed without

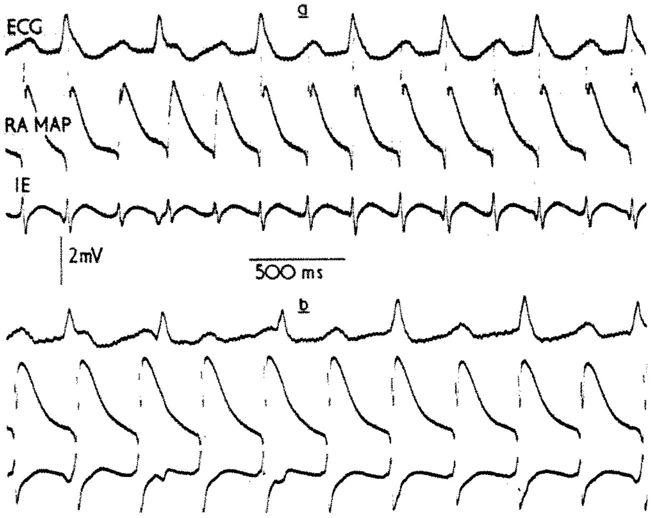

Fig. 5 *Case 1. Persistence of atrial flutter in spite of significant RA MAP prolongation after Bunaphtine (b). IE, intracardiac electrogram.*

conversion to sinus rhythm. The increment of right atrial monophasic action potential total duration was 86·79 per cent and was strongly related to a significant prolongation of cycle length ($y = 210{\cdot}1 + 1{\cdot}37x$; $r = 0{\cdot}99$).

Discussion

A short monophasic action potential duration has been shown to be present in a number of patients with paroxysmal supraventricular arrhythmias (Olsson, 1972; Olsson *et al.*, 1973). In our study only 4 of the 10 patients in sinus rhythm had a rather short right atrial monophasic action potential; the shortest monophasic action potential was found in a patient with a clinical picture of hyperthyroidism in accord with *in vitro* observations (Freedberg *et al.*, 1970; Johnson *et al.*, 1973).

Bunaphtine administration induced a significant prolongation of right atrial monophasic action potential (average 18·38%). As can be seen from Table 2 the largest increment was in patients with a short basic repolarisation (average 29%), while a smaller effect (average 7·1%) resulted when basic right atrial monophasic action potential duration was within normal range. Prolongation of the right atrial monophasic action potential can in part be explained by a significant reduction in heart rate if it occurs (Olsson, 1971); in our study, however, only a slight increase in cycle length was found which was not statistically significant. A clear-cut correlation between right atrial monophasic action potential prolongation and heart rate reduction was evident only in case 1. When the heart rate was maintained constant by atrial pacing (case 11), an increase in total duration of right atrial monophasic action potential (7%) was still seen. This implies that Bunaphtine induces to a certain extent a prolongation of right atrial monophasic action potential as a direct effect. A reduction of relative repolarisation rate of phase 3, strongly correlated to prolongation of right atrial monophasic action potential, was seen after drug infusion in all cases.

The processes governing the shape and duration of repolarisation of cardiac action potential are complex and controversial and have recently been described in a mathematical model (McAllister *et al.*, 1975).

As acetylcholine enhances K^+ permeability in the atrial myocardium (Hoffman and Cranefield, 1960), and vagal stimulation induces a reduction in duration of right atrial monophasic action potential (Samuelsson, 1973) so that the effect of Bunaphtine could be explained as an indirect action on atrial repolarisation by a vagolytic effect; but pharmacological studies contradict this hypothesis (Beani, 1972; Sanna *et al.*, 1974).

The prolongation of repolarisation was most consistent when the basic refractory period was short. In addition to prolonging the duration of atrial repolarisation Bunaphtine also reduced the degree of variation in this duration as recorded from different sites in the same atrium. This normalisation of refractoriness may result in the blocking of re-entry pathways in the atrium leading to an antiarrhythmic effect as a result of the reduction of inhomogeneity of repolarisation. In the 2 patients who developed paroxysmal atrial fibrillation during the procedure (cases 4 and 10), conversion to sinus rhythm was seen during drug infusion, when the duration of right atrial monophasic action potential reached about 200 ms; this value is critical for the re-establishment of sinus rhythm (Gavrilescu and Cotoi, 1972; Olsson, 1972). Immediately after recovery of sinus rhythm the right atrial monophasic action potential duration was still short (Fig. 2d to 3c), and there was a tendency to repetitive arrhythmias. After the final drug-induced normalisation of monophasic action potential duration, full stability of rhythm was achieved (Fig. 2f to 3d). Persistence of atrial flutter in case 1, in spite of the significant prolongation of right atrial monophasic action potential (Fig. 5b), is not clear and seems to contradict the observations in the other 2 patients. It could be related to the lower dose employed, which was sufficient to reduce heart rate. Monophasic action potential prolongation, therefore, could be explained as a rate-dependent modification. Moreover in this patient the effect of other cardioactive drugs was already present.

As stated by Olsson (1971, 1974) the expected variability in a single subject of the atrial monophasic action potential duration between successive applications of the suction electrode can be expressed as a variation coefficient ranging from 0 up to 16·5 per cent. In our patients, with at least 5 applications of the electrode at different sites of the right atrium, an intraindividual variation coefficient ranging from 3·3 to 8·75 per cent was found; this was considered to be an expression of the range of variability of repolarisation duration in the basal condition.

An increased variability or inhomogeneity of the repolarisation of the myocardial fibres may allow development of a re-entry mechanism which could lead to arrhythmias (Sarachek *et al.*, 1972; Wit *et al.*, 1974). In case 9 right atrial monophasic action potential duration was well within normal limits but a wide intraindividual variation coefficient was found (VC = 8·75%), which could account for the clinical picture. After Bunaphtine, the intraindividual variation coefficient was lessened

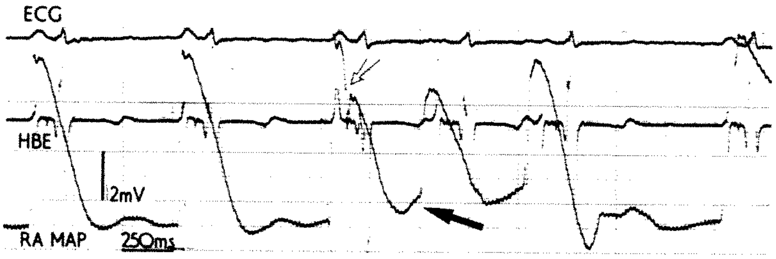

Fig. 6 *Evidence of phase 4 depolarisation (black arrow) during a run of premature atrial contractions. (An atrial fusion beat is also appreciable: white arrow.)*

(VC=5%), suggesting a reduced dispersion of repolarisation; this suggests that an alternative action of the drug is to improve the spread of the excitatory wave-front. To test this hypothesis would require further investigations with a more appropriate technique, such as proposed by Sarachek *et al.* (1972).

Variation coefficients between monophasic action potential durations before and after Bunaphtine were also calculated in individual patients and were employed as an index of the significance of the drug's effect. A higher variation coefficient was found in patients with a shorter duration of right atrial monophasic action potential (average 17·85%), while a lower one was observed in those with a normal repolarisation (average 4·95%).

A slow phase 4 depolarisation, suggestive of latent pacemaker activity (Hoffman and Cranefield, 1960), was found in 3 patients; it was much more evident during a run of premature atrial beats (Fig. 6). After Bunaphtine administration a reduction of prepotential was apparent from inspection of the tracings, but, because of technical limitations, no quantitative evaluation was possible.

The classification of antiarrhythmic drugs is still controversial. Most authors favour an electrophysiological approach (Mason *et al.*, 1973; Sanna *et al.*, 1974; Singh and Hauswirth, 1974; Vaughan Williams, 1975). Monophasic action potential recording alone does not allow an exhaustive evaluation of all properties of an antiarrhythmic drug. It provides information about the local action potential duration, repolarisation uniformity, and instantaneous modifications of cellular refractoriness. Using a pacing technique, an evaluation of the effects of the drug on the effective refractory period/monophasic action potential duration ratio could also be accomplished. Bunaphtine should increase this ratio (Sanna *et al.*, 1974).

In previous electrophysiological clinical studies a depressive effect of Bunaphtine on intra-atrial conduction velocity has been shown (Scibilia *et al.*, 1973; Grazi *et al.*, 1974). The present work appears to confirm, in the human beating heart, what has been observed in *in vitro* investigations (Ferroni *et al.*, 1973), regarding the Bunaphtine-induced prolongation of atrial action potentials. As far as atrial tissue is concerned, therefore, Bunaphtine is a class 3 antiarrhythmic drug according to the classification of Vaughan-Williams (Vaughan Williams, 1975).

References

Beani, L. (1972). Profilo farmacologico di un nuovo antiaritmico: la Bunaftide. *Bollettino della Società Italiana di Cardiologia,* **17,** 1279–1281.

Botti, G. (1972). Un nouveau medicament antiarythmique: la Bunaftine. Experience clinique de plusieurs centres cardiologiques. In Actas del VI Congresso Europeo de Cardiologia, p. 532.

Botti, G., Bonatti, V., Finardi, A., Lazzeroni, E., and Ghinelli, L. (1976). Experimentation clinique de l'action prophylactique et thérapeutique de la Bunaftine sur les arythmies de la phase algue de l'infarctus du myocarde. *Annales de Cardiologie et d'Angeiologie,* **25,** 3.

Cabasson, J., Mellet, J. M., Guimond, C., Bachy, C., Sassine, A., and Puech, P. (1975). L'étude des potentiels de action monophasique du myocarde par voie endocavitaire et ses applications. *Annales de Cardiologie et d'Angéiologie,* **24,** 483.

Fenici, R., Bellocci, F., Zecchi, P., Fiorentini, R., Gabrielli, L., and Carbonin, P. U. (1974a). Effect of Bunaphtine on human atrial MAP. *Acta Medica Romana,* **12,** 75.

Fenici, R., Bellocci, F., Zecchi, P., Gabrielli, L., and Carbonin, P. U. (1973). Monophasic action potential of human heart. Preliminary results with a new technique. *Acta Medica Romana,* **11,** 312,

Fenici, R., Bellocci, F., Zecchi, P., and Zeppilli, P. (1975). La registrazione del potenziale monofasico del cuore destro nell'uomo: suo possibile impiego nella interpretazione delle aritmie. Comunicazione al XXXVI Congresso della Società Italiana di Cardiologia.

Fenici, R., Franceschini, A., Bellocci, F., Gabrielli, L., and Carbonin, P. U. (1974b). Right atrial MAP from human heart: a case of paroxysmal atrial fibrillation. *Acta Medica Romana,* **12,**

Ferroni, A., and Monticelli, G. (1973). Electrophysiological aspects of the action of Bunaphtide on single cardiac muscle fibers. *Pharmacological Research Communications,* **5,** 151–173.

Franchini, G., Storelli, A., Pierfelice, O., Latorre, A., Fiandanese, F., and Rizzon, P. (1974). Attività antiaritmica della Bunaftine. *Bollettino della Società Italiana di Cardiologia,* **19,** 427–433.

Freedberg, A. S., Papp, J. Gy., and Vaughan Williams, E. M. (1970). The effect of altered thyroid state on atrial intracellular potentials. *Journal of Physiology,* **207,** 357–369.

Gavrilescu, S., and Cotoi, S. (1972). Monophasic action potential of right human atrium during atrial flutter and after conversion to sinus rhythm. Argument for re-entry theory. *British Heart Journal,* **34,** 396–402.

Grazi, S., Romano, S., Bonazzi, O., Pozzoni, L., Cavoretto, D., and Gardumi, M. (1975). Studio elettrofisiologico dei disturbi della conduzione intraventricolare nella fase post-acuta dell'infarto del miocardio. Comunicazione al XXXVI Congresso della Società Italiana di Cardiologia.

Grazi, S., Romano, S., Bonazzi, O., Pozzoni, L., Cavoretto, D., Gardumi, M., and Sardella, F. (1974). Effetti di un nuovo farmaco antiaritmico, la Bunaftine, sulla conduzione intra-atriale, atrioventricolare ed intraventricolare dello stimolo. *Cardiologia Pratica,* **25,** 312–216.

Hoffman, B. F., and Cranefield, P. F. (1960). *Electrophysiology of the Heart.* McGraw-Hill, New York.

Hoffman, B. F., Cranefield, P. F., Lepeschkin, E., Surawicz, B., and Herrlich, H. C. (1959). Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. *American Journal of Physiology,* **196,** 1297–1301.

Johnson, P. N., Freedberg, A. S., and Marshall, J. M. (1973). Action of thyroid hormone on the transmembrane potentials from sino-atrial node cells and atrial muscle cells in isolated atria of rabbits. *Cardiology,* **58,** 273–289.

Lotto, A., and Lomanto, B. (1972). Prime esperienze sullo impiego clinico di un nuovo antiaritmico: la Bunaftide. *Bollettino della Società Italiana di Cardiologia,* **17,** 701.

McAllister, R. E., Noble, D., and Tsien, R. W. (1975). Reconstruction of the electrical activity of cardiac Purkinje fibres. *Journal of Physiology,* **251,** 1–59.

Masini, G., Cuccu, E., and Zanetti, L. (1972). Sull' impiego della Bunaftine nel trattamento ambulatoriale di alcuni disturbi del ritmo. *Bollettino della Società Italiana di Cardiologia,* **17,** 12.

Mason, D., Amsterdam, E. A., Massumi, R. A., Mansur, E. J., Hughes, J. L., III., and Zelis, R. (1973). Combined actions of antiarrhythmic drugs. Electrophysiological and therapeutic consideration. In *Cardiac Arrhythmias,* p. 531. Ed. by L. S. Dreifus and W. Likoff. Grune and Stratton, New York.

Olsson, S. B. (1971). *Monophasic Action Potential of Right Heart. Suction Electrode Method in Clinical Investigation.* Elanders Boktrykery Ab, Goteborg.

Olsson, S. B. (1972). Recording of monophasic action potentials in the study of atrial dysrhythmias. *Giornale Italiano di Cardiologia,* **2,** 536–541.

Olsson, S. B. (1974). Atrial repolarization in man. Effect of beta-receptor blockade. *British Heart Journal,* **36,** 806–810.

Olsson, S. B., Brorson, L., and Varnauskas, E. (1973). Class 3 antiarrhythmic action in man. Observations from monophasic action potential recordings and amiodarone treatment. *British Heart Journal,* **35,** 1255–1259.

Samuelsson, R. (1973). Effects of severe systemic hypoxia on myocardial excitation. *Acta Physiologica Scandinavica,* **88,** 267–280.

Sanna, G. P., Lomanto, B., and Rossi, A. (1974). Basi elettrofisiologiche dell'azione dei farmaci antiaritmici. *Minerva Cardioangiologica,* **22,** 731–758.

Sarachek, N. S., Roberts, J., and James, J. L. (1972). A new method to measure non-uniformity in the intact heart. *Journal of Electrocardiology,* **5,** 341–348.

Scibilia, G., Bonatti, V., Pavarani, A., Tagliavini, S., and Botti, G. (1973). Effetto sul fascio di His di una nuova sostanza antiaritmica, la Bunaftine. *Cardiologia Pratica,* **24,** 79–84.

Shabetai, R., Surawicz, B., and Hammill, W. (1968). Monophasic action potentials in man. *Circulation,* **38,** 341–352.

Singh, B. N., and Hauswirth, O. (1974). Comparative mechanisms of action of antiarrhythmic drugs. *American Heart Journal,* **87,** 367–382.

Vaughan Williams, E. M. (1975). Classification of antidysrhythmic drugs. *Pharmacology and Therapeutics B,* **1,** 115–138.

Vegis, D. (1975). La Bunaftine nel trattamento delle aritmie. *Cardiologia Pratica,* **26,** 29.

Wit, A., Rosen, M., and Hoffman, B. (1974). Electrophysiology and pharmacology of cardiac arrhythmias. II. Relationship of normal and abnormal electrical activity of cardiac fibers to the genesis of arrhythmias. B. Re-entry. Section 1. *American Heart Journal,* **88,** 664–670.

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The Elag-Koln automatic blood pressure recorder
A clinical appraisal

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The performance of an Elag-Köln semiautomatic blood pressure recorder was compared with the London School of Hygiene mercury sphygmomanometer in 24 subjects providing a wide range of blood pressure measurements. Readings with the two instruments correlated highly (for systole, $r=0{\cdot}99$; for diastole phase 4, $r=0{\cdot}97$; for diastole phase 5, $r=0{\cdot}98$), and the slopes of the regressions did not differ significantly from unity. Elag-Köln measurements were higher for systole (mean difference 3·7 mmHg, $P<0{\cdot}001$) and diastole phase 5 (mean difference 7·4 mmHg, $P<0{\cdot}001$), but agreed closely with diastole phase 4 readings with the London School of Hygiene instrument. The Elag-Köln recorder tested was compact, easy to use, and had acceptable accuracy. This type of instrument deserves further testing to examine its suitability for general use.

The importance of accuracy of blood pressure measurement in routine practice, in epidemiological surveys, and in clinical trials has been stressed (Rose *et al.*, 1964; King, 1969; Thulin *et al.*, 1975). Measurement errors may arise from inaccuracy of the instrument (Thulin *et al.*, 1975; Conceicao *et al.*, 1976) or from factors related to the observer (Rose *et al.*, 1964). With auscultatory methods of measurement, the principal sources of observer error are terminal digit preference, prejudice related to specific blood pressure values, and difficulty in interpretation of the Korotkoff sounds (Rose *et al.*, 1964). Several devices have been developed to avoid digit preference and prejudice (Rose *et al.*, 1964; Wright and Dore, 1970). To remove errors in the interpretation of the auscultatory phases, semiautomatic machines have been developed, but their performance has often proved unsatisfactory (Thulin *et al.*, 1975). Labarthe *et al.* (1973) evaluated 5 automatic devices and found that none of them was an adequate replacement for the mercury sphygmomanometer.

In the present study we have assessed the Elag-Köln automatic blood pressure recorder using a London School of Hygiene (LSH) sphygmomanometer as the standard for comparison.

Methods

RECORDING DEVICES

An Elag-Köln sphygmomanometer[1] (Fig. 1) without the automatic print-out recorder, and a standard London School of Hygiene (LSH), random zero, mercury sphygmomanometer (Rose *et al.*, 1964) were compared. The Elag-Köln cuff contains a rubber air chamber which transmits pressure pulses from the brachial artery region to an amplifier and the Korotkoff phases are transformed into optical and acoustic displays. Inflation is by a high speed pump to a preselected pressure and deflation rate can be varied. As the manometer needle descends, the appearance of a flashing light and an accompanying bleep (which can be muted) indicates systolic pressure. The flash and bleep continue synchronously with the pulse beat until diastole is reached. Pulse frequency is also displayed. For this study, the rate of fall of pressure was fixed at 2 mmHg/s for the LSH machine, and as close as possible to this figure on the Elag-Köln. The pressure readings on the latter device (checked against a mercury manometer) were found to be accurate.

SUBJECTS AND PROCEDURE

Twenty hospital inpatients and 4 healthy subjects were selected to provide a wide range of blood pressures. The inpatients had hypertension or were general medical patients. One had atrial fibrillation and one pulsus paradoxus. Pressures were measured by two physicians experienced in the use of both devices. Each subject remained supine for at least 10 minutes, after which the blood pressure was recorded in either arm by both observers and with both devices (i.e. 4 pairs of simultaneous readings). The cuffs were removed and reapplied for each individual reading. The Elag-Köln scale read to the

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[1] Inh. J. Klein, 5 köln 30 (Ehrenfeld) Overbeckstr. 2-4, Germany. British distributors: Andrew Stephens, 41 Dickson Road, Blackpool FY1 2AP, England.

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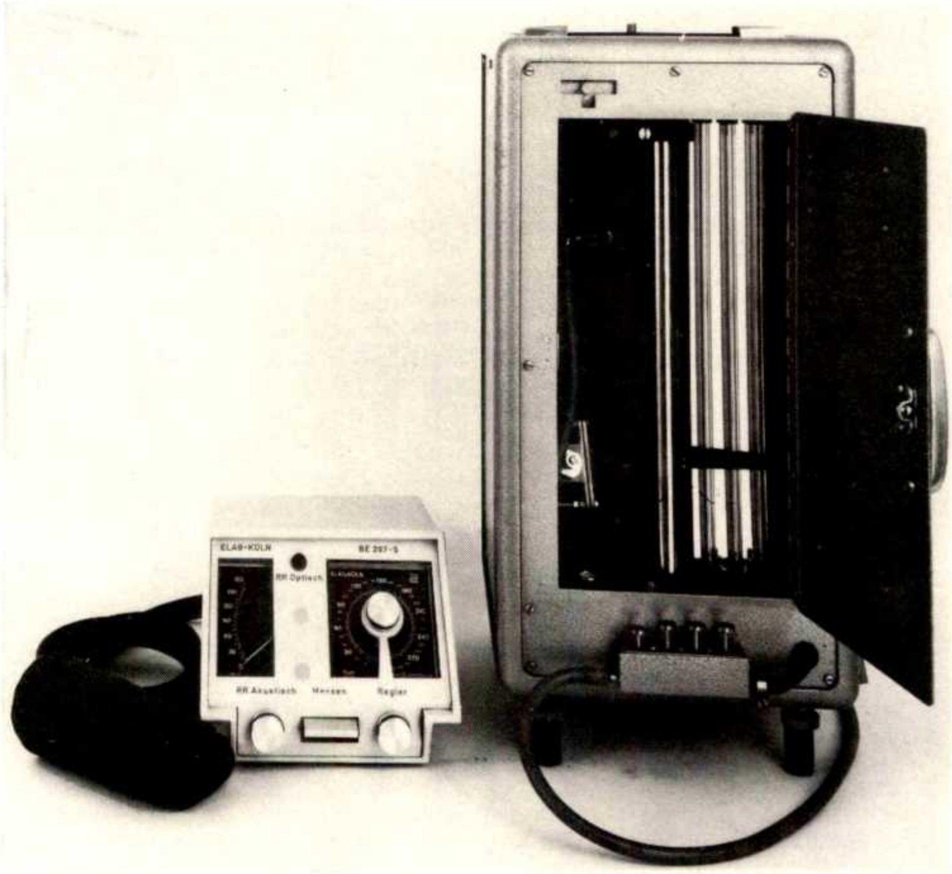

Fig. 1 *The Elag-Köln recorder (left) shown beside the London School of Hygiene sphygmomanometer. Blood pressure is read from the right hand dial. Inflation pressure is preselected using the control knob at the centre of this dial, and automatic inflation is initiated by pressing the switch (Messen). A needle then descends the scale during deflation. Deflation rate can be varied (Regler). A flashing light (RR Optisch) and bleep appear at systole, and stop at diastole. Pulse rate is displayed on the dial on the left. The volume of the bleep is adjustable (RR Akustisch).*

nearest 2 mmHg and recorded a single diastolic end-point. The LSH machine was calibrated to 1 mmHg, and both diastolic end-points (phases 4 and 5) were noted.

DESIGN AND ANALYSIS

For each subject, 4 pairs of simultaneous measurements with the 2 machines were made, and the order of observer—machine—arm was varied systematically in successive subjects. With this scheme, the mean of 4 Elag-Köln readings versus the mean of 4 LSH readings in each patient gave a comparison of the machines which was not biased by observer, by arm, or by measurement sequence. The results from the two devices were compared using Student's t test for paired observations. Regressions were tested to determine whether they deviated significantly from a slope of one.

Results

For systolic blood pressure, the two machines showed a high correlation ($r=0{\cdot}99$; Fig. 2) over a wide range of readings. The slope of the regression was 0·99, but the Elag-Köln values were significantly higher than those with the LSH machine (mean difference 3·7 mmHg; $t=3{\cdot}97$, $P<0{\cdot}001$). Elag-Köln diastolic blood pressure correlated highly with both phase 5 ($r=0{\cdot}98$; slope 1·05) and phase 4 ($r=0{\cdot}97$; slope 0·96) readings with the LSH machine. In absolute terms, Elag-Köln diastolic readings were closer to phase 4

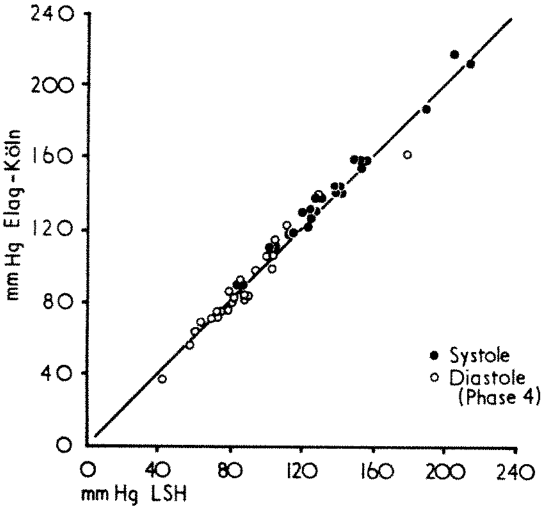

Fig. 2 *Correlation between readings from the London School of Hygiene sphygmomanometer and Elag-Köln machine. Each point represents the mean of 4 readings (2 observers measuring blood pressure in both arms) with each of the two measuring devices in an individual patient.*

LSH pressures (mean 0·5 mmHg higher for the Elag-Köln), and were significantly higher than phase 5 (mean difference 7·4 mmHg; $t=7{\cdot}15$, $P<0{\cdot}001$).

The experimental design was such that 75 per cent of Elag-Köln blood pressure measurements were made with knowledge of a previous reading with either machine in the same patient. Since reading of the Elag-Köln instrument could be subject to observer bias, the correlations between blood pressure measurements with the two devices might be falsely high. We, therefore, correlated those blood pressure readings measured first with the Elag-Köln device against the subsequent blood pressure reading made in that patient by the same observer, on the same arm, but with the LSH machine. This correlation is entirely free of observer bias, but might be weakened because the measurements with the two machines were not simultaneous (LSH readings 3 to 5 minutes after Elag-Köln readings). Nevertheless the correlation between the two instruments remained high (systole, $r=0{\cdot}95$, slope 0·98; diastole phase 5, $r=0{\cdot}94$, slope 0·95; $n=24$).

The correlation between observers with the LSH machine was close (systole $r=0{\cdot}96$; diastole, phase 5, $r=0{\cdot}97$) but was even closer with the Elag-Köln machine (systole $r=0{\cdot}98$; diastole $r=0{\cdot}99$). Examination of the consistency of each observer with each machine was weakened by a significant difference in systolic readings between the two arms (right arm higher by 2·7 mmHg; $t=2{\cdot}75$, $P<0{\cdot}02$). Within-observer correlations were similar for each machine (for LSH machine, r between 0·94 to 0·98; for Elag-Köln, r between 0·95 to 0·96). Since the Elag-Köln measurements were read visually the results were examined for evidence of terminal digit bias. The distribution of terminal digits did not differ significantly from the expected distribution for either observer ($P>0{\cdot}1$).

Both observers thought the Elag-Köln device had certain advantages over the LSH machine. Measurement of blood pressure was quicker and easier particularly in noisy surroundings, and the Elag-Köln was eminently more portable (weight 3·5 kg, compared to 16·5 kg for the LSH machine). Placement of the air-chamber of the Elag-Köln cuff over the brachial artery caused no problem though we have not studied systematically the effect of inaccurate cuff placement. The rate of cuff deflation was difficult to stabilise because of the extreme sensitivity of the manual control. Further, it was noted that with deflation, the rate of fall of pressure was not uniform, being faster at high pressures and slowing as lower values were registered. The need for a source of electricity to operate the Elag-Köln could be a drawback in some situations.

Discussion

The accuracy of the Elag-Köln machine tested was acceptable, as judged by the high correlations with LSH sphygmomanometer results. Systolic blood pressure readings were on average 3·7 mmHg higher with the Elag-Köln. Since auscultatory measurements of systole are in general a few mmHg lower than direct readings (Pickering, 1968), it is likely that the Elag-Köln values were nearer true systole than LSH recordings. The Elag-Köln diastolic readings correspond to phase 4 readings by the auscultatory method, and correlated highly with phase 5 readings though measuring on average 7·4 mmHg higher. The Elag-Köln was simpler and quicker to use than the LSH sphygmomanometer, and it was considerably less cumbersome. Use of the print-out recorder (which is optional) should eliminate any risk of terminal digit preference and prejudice against certain readings.

If the performance of the machine we tested is representative and if the device proves robust in everyday use, then the Elag-Köln recorder should be of great value in ordinary hospital practice and for epidemiological surveys. The ability to repeat blood pressure measurements simply and rapidly would be useful in intensive care units and during diagnostic or therapeutic procedures.

We wish to thank Mr. W. C. B. Brown and Dr. A. F. Lever for helpful discussion. M.G.N. is recipient of a New Zealand Medical Research Council Overseas Fellowship. L.E.R. is a Searle Research Fellow in Clinical Pharmacology.

References

Conceicao, S., Ward, M. K., and Kerr, D. N. S. (1976). Defects in sphygmomanometers: an important source of error in blood pressure recording. *British Medical Journal*, **1**, 886–888.

King, G. E. (1969). Taking the blood pressure. *Journal of the American Medical Association*, **209**, 1902–1904.

Labarthe, D. R., Hawkins, C. M., and Remington, R. D. (1973). Evaluation of performance of selected devices for measuring blood pressure. *American Journal of Cardiology*, **32**, 546–553.

Pickering, G. (1968). *High Blood Pressure*, 2nd ed., p. 9. Churchill, London.

Rose, G. A., Holland, W. W., and Crowley, E. A. (1964). A sphygmomanometer for epidemiologists. *Lancet*, **1**, 296–300.

Thulin, T., Andersson, G., and Scherstén, B. (1975). Measurement of blood pressure—a routine test in need of standardization. *Postgraduate Medical Journal*, **51**, 390–395.

Wright, B. M., and Dore, C. F. (1970). A random zero sphygmomanometer. *Lancet*, **1**, 337–338.

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Baroreflex sensitivity and cardiopulmonary blood volume in normotensive and hypertensive patients

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Baroreflex sensitivity and cardiopulmonary blood volume were determined in 95 men, including normotensive and hypertensive subjects with normal renal function and balanced sodium intake and urinary output. Baroreflex sensitivity was estimated by determining the slope of the regression line relating the increase of systolic pressure to the cardiac slowing after transient rises of arterial pressure. A technique of gradual atropinisation was used to evaluate the parasympathetic mediated component of the reflex. With this method, it was possible to calculate the exact atropine dose abolishing the reflex sensitivity. This index was not dependent on age. It was negatively correlated to the diastolic pressure in normotensive patients but not in hypertensive patients. The ratio between the cardiopulmonary and the total blood volume was considered as an index of sympathetic venous tone. This ratio was positively correlated to the diastolic pressure in normotensive patients, but not in hypertensive patients. This study strongly suggests that a precise sympathetic-parasympathetic balance existed in the normotensive patients. This balance was disrupted in the hypertensive patients pointing to abnormalities in the autonomic nervous system of permanently hypertensive patients.

Increasing evidence suggests that essential hypertension is associated with a pronounced disturbance of the autonomic nervous system. Profound changes in the metabolism and the activity of the autonomic nerves have been shown in various models of experimental hypertension (Chalmers, 1975; Haeusler, 1975; Reid *et al.*, 1975). No comparable information has been obtained in man, because of the difficulty in assessing the sympathetic and parasympathetic status.

Although the sympathetic system in essential hypertension has been extensively studied, few quantitative estimations are available. Nevertheless, the evidence for an overactive sympathetic activity remains controversial (Louis *et al.*, 1974; Berglund *et al.*, 1976). Among the haemodynamic values, heart rate, response to tilt, and basal cardiopulmonary blood volume have been proposed as indices of sympathetic activity (Frohlich *et al.*, 1967; DeQuattro and Miura, 1973; Ellis and Julius, 1973; Safar *et al.*, 1975). Information concerning the parasympathetic system is more difficult to obtain, because of the lack of adequate indices. However, a possible approach for assessment of parasympathetic function results from the evaluation of baroreceptor responsiveness to rising arterial pressure. Recent studies have shown that baroreflex bradycardia is mediated predominantly by the parasympathetic (Eckberg *et al.*, 1971; Pickering *et al.*, 1972).

In order to help elucidate the role of the parasympathetic system in hypertension, we have studied, in 95 normal and essential hypertensive subjects, the baroreflex cardiac slowing consecutive to a transient rise of arterial pressure. A special method is suggested to enable a quantitative evaluation of the baroreflex parasympathetic component to be made. In some patients, sympathetic activity was also estimated by the measurement of the basal cardiopulmonary blood volume.

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Subjects and methods

SUBJECTS

Ninety-five subjects [mean age: 36 ±4 years (±1 standard error of the mean)] were included in this study. The diastolic pressure recordings of outpatients ranged between 60 and 140 mmHg, corresponding to normal subjects or patients referred to the hospital because of high blood pressure.

The subjects were untreated or had discontinued their therapy at least four weeks before the study. They were admitted to hospital for 6 days and placed on a sodium diet of 100 mmol per day.

All the patients referred because of suspected hypertension were submitted to extensive investigations including blood and urinary electrolytes, catecholamine determinations, endogenous creatinine clearance, timed intravenous urography, and/or renal arteriography. All of these patients were listed as essential hypertensives. None had neurological or cardiac involvement; mild to moderate left ventricular hypertrophy was observed in 41 patients. Mean creatinine clearance was 86 ± 12 ml/min per m^2.

Consent for investigations was obtained after detailed description of the procedure, and the procedure was approved by INSERM (Institut National de la Santé et de la Recherche Médicale).

ESTIMATION OF BAROREFLEX SENSITIVITY

Seventy-two patients were studied in the supine position without premedication, on the third day in hospital. Under local procaine anaesthesia, a polyethylene catheter was introduced into the right brachial artery for continuous measurement of the intra-arterial blood pressure. Arterial pressure, respiratory movements obtained by a pneumograph, and electrocardiogram were recorded simultaneously on a multichannel oscillograph (Siemens). A second cannula was inserted in a median antecubital vein and allowed the multiple bolus injections necessary for the baroreflex sensitivity estimation.

The basal sensitivity of the baroreflex was determined by using the technique of Smyth *et al.* (1969). Several bolus intravenous injections of 50 to 200 μg phenylephrine were given to induce a transient rise of the arterial pressure by 20 to 40 mmHg. The systolic blood pressure of each beat was plotted against the second interval RR (in ms) following it. Plotting was started 10 beats after the end of injection until just after the peak systolic pressure; RR intervals during inspiration were not included in order to reduce the effects of sinus arrhythmia. Linear relations between RR intervals and systolic blood pressure were observed and the RR systolic pressure correlations with a P value of less than 0·02 were discounted. The reflex sensitivity was expressed as the slope of the regression line (milliseconds increase in RR interval per mmHg rise in systolic blood pressure). The mean value of two or three slopes was used as estimation of the basal sensitivity and called 'basal slope'.

The baroreflex sensitivity tested by means of phenylephrine was also determined after propranolol and after propranolol plus atropine by intravenous injection.

Beta adrenergic blockade by propranolol was induced before atropinisation. The dose of propranolol (0·2 mg/kg body weight) was known to produce effective beta-adrenergic blockade (Jose and Taylor, 1969). The baroreflex slope was calculated 10 minutes after the intravenous injection of propranolol and was called 'slope after propranolol'.

Parasympathetic blockade by atropine was induced after propranolol blockade. As well established in the literature, total parasympathetic blockade can be obtained by the intravenous injection of 0·04 mg/kg atropine sulphate (Jose and Taylor, 1969; Eckberg *et al.*, 1971; Pickering *et al.*, 1972). However, the corresponding baroreflex response is almost abolished and does not, therefore, allow determination of the precise level of parasympathetic blockade. In the present study, progressive parasympathetic blockade was used by dividing the total dose of atropine of 0·04 mg/kg into 6 successive and cumulative doses; individual doses were injected intravenously every 10 minutes. The baroreflex slope was repeatedly determined during this gradual atropinisation as follows: each partial dose of atropine was followed 5 minutes later by the determination of the slope; each slope determination was followed by 5 minutes of rest in order to eliminate any remaining effect of the phenylephrine. This procedure was repeated 6 times. Through all this period, no significant change in blood pressure was observed. The slopes so calculated declined as progressive parasympatoetic blockade occurred. The slope was plotted semilogarithmically against the immediate preceding dose of atropine expressed per kilogram of body weight. A significant negative linear correlation was found between the slope and the log atropine dose (Fig. 1). By means of this log dose slope curve, the dose of atropine corresponding to a zero slope was calculated. This dose was called 'atropine blocking dose' and was used as a quantitative evaluation of the parasympathetic blockade level (Fig. 1).

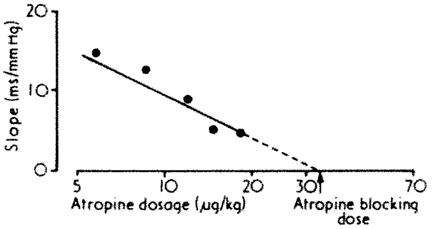

Fig. 1 *Dose response curve between the atropine dose and the slope of the baroreflex (semilogarithmic scale). The arrow corresponds to the so-called 'atropine blocking dose' (see text).*

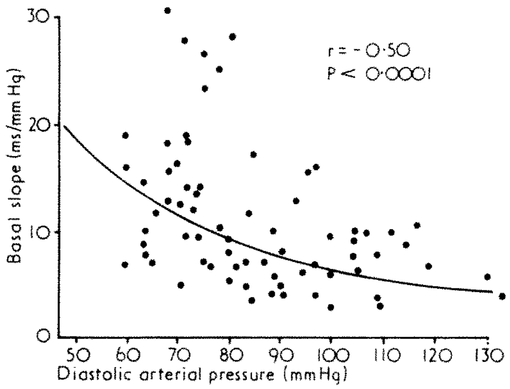

Fig. 2 *Relation between the basal slope and the diastolic arterial pressure in the overall population. The hyperbolic model existed even with the semilogarithmic scale.*

CARDIOPULMONARY BLOOD VOLUME ESTIMATION

Cardiopulmonary blood volume (CPBV) was measured on the third day in hospital in 95 patients, as previously described (Safar *et al.*, 1975). Two polyethylene catheters were introduced, the first into the right brachial artery and the other into a median antecubital vein. They were respectively advanced under fluoroscopic control into the aortic arch and the main pulmonary artery. Cardiopulmonary blood volume was expressed as the volume between the main pulmonary artery and the aortic root immediately distal to the aortic valves. It was calculated by the Stewart-Hamilton method (Hamilton *et al.*, 1932) as following: CPBV (ml/kg) = CI (ml/min/kg) × Tm (s) (PA-Ar); Tm(PA-Ar) equals mean transit time in seconds from the pulmonary artery (PA) to the tip of the arterial catheter (Ar).

Total blood volume (TBV) was simultaneously measured by radio-iodinated albumin, as previously described (Safar *et al.*, 1975). The CPBV/TBV ratio was calculated. This ratio represented the fraction of total blood volume in the heart and lungs and was independent of normalisation.

Table *Relation between diastolic arterial pressure and baroreflex slope, before and after propranolol: a hyperbolic model ($Y = a/X + b$) was presented*

Y	*X*	*r value*	*P value* *(n = 72)*	*Regression coefficient (± 1 standard error of the slope)*	*Intercept*
Slope basal value (ms/mmHg)	Diastolic pressure (mmHg)	–0·50	< 0·0001	51·4 ± 7·2	0·34
Slope after propranolol (ms/mmHg)	Diastolic pressure (mmHg)	–0·41	< 0·0001	46·2 ± 9·3	0·51

HAEMODYNAMIC CLASSIFICATION OF PATIENTS

The criterion for the classification of the patients was the diastolic intra-arterial pressure recorded during cardiac output determination. All blood pressure determinations were made with the subject in the resting position after a period of familiarisation. Any patient with adverse reactions was eliminated; in no instance was the basal blood pressure value significantly different on repeat measurements.

The intra-arterial diastolic pressure ranged from 60 to 135 mmHg and presented a continuous series (Pickering, 1968) which was arbitrarily divided into 2 groups. The patients were considered as normotensive when the blood pressure recording showed a diastolic pressure of 90 mmHg or less. The patients were considered as hypertensive when the diastolic pressure was above this value. Statistical analysis using classical methods (Croxton and Cowden, 1939) (difference of means, correlations and regression) was performed in the 2 groups of patients.

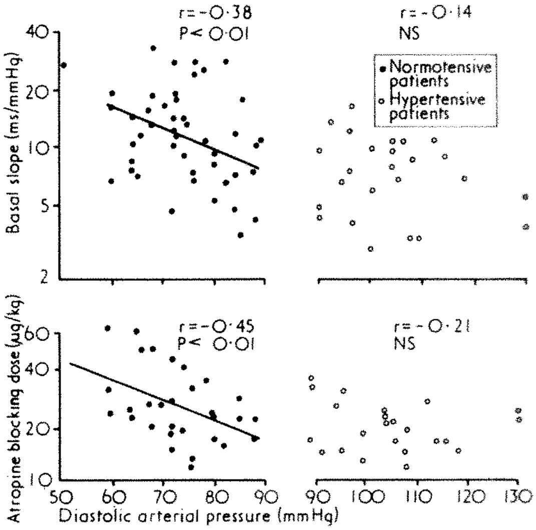

Fig. 3 *Correlations: (i) between the basal slope and the diastolic arterial pressure, and (ii) between the atropine blocking dose and the diastolic arterial pressure, in normotensive and hypertensive patients (semilogarithmic scale).*

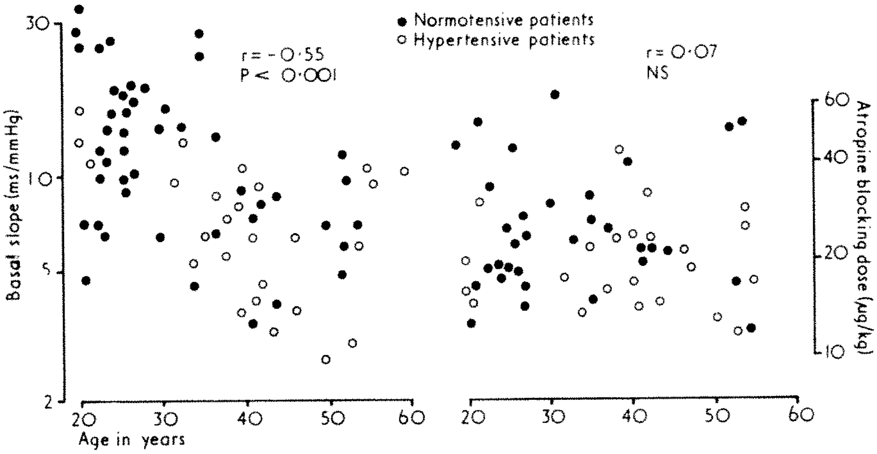

Fig. 4 *Correlations: (i) between the basal slope and age, and (ii) between the atropine blocking dose and age, in the overall population (semilogarithmic scale). Note that the basal slope was negatively correlated to the age both in normotensive and hypertensive patients, while the atropine blocking dose was not.*

Results

I—BAROREFLEX SENSITIVITY ESTIMATION

Basal slope in overall population (72 patients)

The basal slope was negatively correlated to the diastolic arterial pressure ($P < 0{\cdot}001$) (Fig. 2). The correlation existed even for a constant age.

The relation was curvilinear rather than linear. The major model of the curve was hyperbolic (Fig. 2). This model existed even on a semilogarithmic scale. Propranolol did not modify the regression curve (Table).

Comparison between normotensive and hypertensive patients

The basal slope in the normotensive group was negatively correlated to the diastolic pressure ($P < 0{\cdot}01$) (Fig. 3). No correlation was observed in the hypertensive group (Fig. 3).

Age was negatively correlated to the basal slope, both in normotensive ($P < 0{\cdot}001$) and hypertensive subjects ($P < 0{\cdot}001$) (Fig. 4).

The atropine blocking dose was negatively correlated to the diastolic pressure in the normotensive group ($P < 0{\cdot}001$) (Fig. 3) but not in the hypertensive group (Fig. 3). There was no correlation between age and atropine blocking dose in the overall population or in each subgroup (Fig. 4).

II—CARDIOPULMONARY BLOOD VOLUME ESTIMATION

In normotensive patients, a significant positive correlation was observed between the CPBV/TBV ratio and the diastolic arterial pressure ($P < 0{\cdot}01$) (Fig. 5). This correlation was not age dependent (partial correlation). In hypertensive subjects no correlation existed between CPBV/TBV ratio and diastolic pressure (Fig. 5). No significant difference existed in the cardiopulmonary blood volumes mean values of normotensive and hypertensive patients.

Discussion

BAROREFLEX SENSITIVITY ESTIMATION

The results of this study indicate that baroreflex sensitivity decreases in parallel with the rise in blood pressure, in agreement with other reports

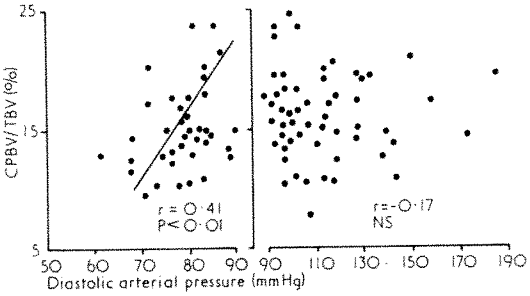

Fig. 5 *Correlation between the CPBV/TBV ratio and the diastolic arterial pressure in normotensive and hypertensive patients. CPBV, cardiopulmonary blood volume; TBV, total blood volume.*

(Bristow *et al.*, 1969; Gribbin *et al.*, 1971; Takeshita *et al.*, 1975). When analysing the overall population, the regression line between the baroreflex sensitivity and the diastolic pressure is of hyperbolic type. This finding is consistent with published studies, in which the plot of baroreflex sensitivity against pressure is curvilinear rather than linear (Bristow *et al.*, 1971; Gribbin *et al.*, 1971). Such a hyperbolic curve points to a defect in the reduction of the slope with increasing pressure in the high blood pressure range. Analysis of the overall population is in agreement with a smooth graduation between normal and high blood pressure as reported in large epidemiological studies (Pickering, 1968). However, in order to help elucidate the mechanisms responsible for the slope decline, the subjects were arbitrarily divided into two groups: normotensive and hypertensive patients.

Two mechanisms are commonly invoked to explain the reduced baroreflex response with increase in blood pressure:

The first is the reduction of the baroreceptors arterial wall compliance resulting from increasing stiffness by medial hypertrophy, arteriosclerosis, or increase in the sodium and water contents or the arterial walls (Bader, 1967). In this study, this hypothesis is supported by the finding that increasing age is associated with the reduction of baroreflex sensitivity. Such a result is observed both in normotensive and hypertensive patients, as previously shown by others (Gribbin *et al.*, 1971).

The second possibility for the diminished baroreflex response is parasympathetic nerve depression (Bristow *et al.*, 1971; Eckberg *et al.*, 1971; Pickering *et al.*, 1972). In the present report, a special method using gradual atropinisation was used to determine the atropine dose required to block completely the parasympathetic component of the baroreflex. Beta-adrenergic blockade, intended to eliminate any sympathetic interaction, did not modify the baroreflex responsiveness. The finding that the atropine blocking dose decreases with increasing diastolic pressure indicates a parasympathetic tone depression consecutive to the rise in blood pressure. This result is seen in normotensive subjects, but not in hypertensive groups. However, the possibility remains that the parasympathetic nerve depression may reflect a reduction in compliance in the baroreceptor region and hence less baroreflex buffering of sympathetic tone, and reflex increase of parasympathetic tone. This mechanism should affect mainly the older subjects with higher pressures in whom the baroreceptor arterial wall is likely to be stiffer. The lack of correlation of the atropine blocking dose with age excludes this hypothesis. This latter is not in agreement with previous studies (Nalefski and Brown, 1950) suggesting that vagal tone diminishes progressively with age. However, the decreased vagal tone with age in these reports was only based on the changes in heart rate after atropine administration, whereas the proposed atropine blocking dose is estimated from the overall baroreceptor arc reflex and so provides a more reliable index.

Of the two mechanisms responsible for the slope decline, arterial baroreceptor compliance appears to play a role in both normotensive and hypertensive subjects. In contrast, the parasympathetic depression of the baroreflex with increased pressure exists only in the normotensive patients. The lack of such a phenomenon in hypertensives points to a malfunction of the parasympathetic nervous system in these patients.

CARDIOPULMONARY BLOOD VOLUME ESTIMATION

The cardiopulmonary blood volume, by reflecting the fraction of blood in the lungs and the heart, is mainly determined by the compliance of the capacitance vessels in the peripheral circulatory system. It has been well established that the constriction of capacitance vessels is related to sympathetic venous tone (Yu, 1969). In addition, the cardiopulmonary blood volume has been shown to be strongly correlated to major biological sympathetic indices, such as plasma dopamine-beta-hydroxylase activity and vascular reactivity to norepinephrine in borderline hypertension, which is characterised by sympathetic hyperactivity (Safar *et al.*, 1975; Alexandre *et al.*, 1975). Thus, it can be tentatively concluded that determination of the cardiopulmonary blood volume constitutes an indirect estimation of sympathetic venous tone.

According to the above statement, the finding that the CPBV/TBV ratio increases in parallel with the diastolic pressure suggests the existence of a common sympathetic influence on these two factors. These results are observed in the normotensive, but not in the hypertensive group. Since the hypertensive patients had no evidence of cardiac impairment, it does not seem likely that a change of the compliance of the left ventricle could explain the lack of correlation. Thus, the disappearance in the correlation between diastolic pressure and CPBV/TBV ratio in hypertensive group suggests a disrupted sympathetic mechanism in these patients.

PARASYMPATHETIC AND SYMPATHETIC BALANCE IN NORMOTENSIVE AND HYPERTENSIVE SUBJECTS

Previous studies provide evidence of a parasympathetic-sympathetic balance. Central or peripheral autonomic interactions modulate the baroreflex (Gellhorn, 1964; Glick and Braunwald, 1965; Warner and Russell, 1969; Klevans and Gebber, 1970; DeQuattro and Miura, 1973). The attenuation of the baroreflex sensitivity in states of heightened sympathetic activity such as exercise (Bristow *et al.*, 1971; Pickering *et al.*, 1972) and heart failure (Eckberg *et al.*, 1971) are considered to be the result of central modulation of the reflex arc rather than the direct interaction of sympathetic and parasympathetic activities peripherally. Julius *et al.* (1971) reported a simultaneous increase of sympathetic activity and decrease of parasympathetic tone in patients with borderline hypertension.

The present study is in agreement with these findings. In the normotensive group, the increase in pressure is related both to: (i) a decrease in the atropine blocking dose and, (ii) an increase in the CPBV/TBV ratio, so evoking a precise sympathetic-parasympathetic balance. Such a balance is disrupted in hypertensive patients, indicating an alteration in both sympathetic and parasympathetic controls. This observation is consistent with previous experimental studies (Chalmers, 1975; Reid *et al.*, 1975) which have shown that impairment of the autonomic nervous system, particularly in its central connections, might represent a trigger mechanism for the initiation and the maintenance of hypertension.

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References

Alexandre, J. M., London, G. M., Chevillard, C., Lemaire, P., Safar, M. E., and Weiss, Y. (1975). The meaning of dopamine beta hydroxylase in essential hypertension. *Clinical Science and Molecular Medicine,* **49,** 573–579.

Bader, H. (1967). Dependence of wall stress in the human thoracic aorta on age and pressure. *Circulation Research,* **20,** 354–361.

Berglund, G., Wallentin, I., Wikstrand, J., and Wilhelmsen, L. (1976). Sodium excretion and sympathetic activity in relation to severity of hypertensive disease. *Lancet,* **1,** 324–328.

Bristow, J. D., Brown, E. B., Jr., Cunningham, D. J. C., Howson, M. G., Strange Petersen, E., Pickering, T. G., and Sleight, P. (1971). Effect of bicycling on the baroreflex regulation of pulse interval. *Circulation Research,* **28,** 582–592.

Bristow, J. D., Honour, A. J., Pickering, G. W., Sleight, P., and Smyth, H. S. (1969). Diminished baroreflex sensitivity in high blood pressure. *Circulation,* **39,** 48–54.

Chalmers, J. P. (1975). Brain amines and models of experimental hypertension. *Circulation Research,* **36,** 469–480.

Croxton, F. E., and Cowden, D. J. (1939). *Applied General Statistics,* p. 544. Prentice Hall, New York.

DeQuattro, V., and Miura, Y. (1973). Neurogenic factors in human hypertension: mechanism or myth? *American Journal of Medicine,* **55,** 362–378.

Eckberg, D. L., Drabinsky, M., and Braunwald, E. (1971). Defective cardiac parasympathetic control in patients with heart disease. *New England Journal of Medicine,* **285,** 877–883.

Ellis, C. N., and Julius, S. (1973). Role of central blood volume in hyperkinetic borderline hypertension. *British Heart Journal,* **35,** 450–455.

Frohlich, E. D., Tarazi, R. C., Ulrych, M., Dustan, H. P., and Page, I. H. (1967). Tilt test for investigating a neural component in hypertension. Its correlation with clinical characteristics. *Circulation,* **36,** 387–393.

Gellhorn, E. (1964). The significance of the state of the central autonomic nervous system for quantitative and qualitative aspects of some cardiovascular reactions. *American Heart Journal,* **67,** 106–120.

Glick, G., and Braunwald, E. (1965). Relative roles of the sympathetic and parasympathetic nervous systems in the reflex control of heart rate. *Circulation Research,* **16,** 363–375.

Gribbin, B., Pickering, T. G., Sleight, P., and Peto, R. (1971). Effect of age and high blood pressure on baroreflex sensitivity in man. *Circulation Research,* **29,** 424–431.

Haeusler, G. (1975). Cardiovascular regulation by central adrenergic mechanisms and its alteration by hypotensive drugs. *Circulation Research,* **36–37,** Suppl. I, 223–232.

Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G. (1932). Studies on the circulation, further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions. *American Journal of Physiology,* **99,** 534–551.

Jose, A. D., and Taylor, R. R. (1969). Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. *Journal of Clinical Investigation,* **48,** 2019–2031.

Julius, S., Pascual, A. V., and London, R. (1971). Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation,* **44,** 413–418.

Klevans, L. R., and Gebber, G. L. (1970). Facilitatory forebrain influence on cardiac component of baroreceptor reflexes. *American Journal of Physiology,* **219,** 1235–1241.

Louis, W. J., Doyle, A. E., Anavekar, S. N., Johnston, C. I., Geffen, L. B., and Rush, R. (1974). Plasma catecholamine, dopamine-beta-hydroxylase, and renin levels in essential hypertension. *Circulation Research,* **34–35,** Suppl. I, 57–64.

Nalefski, L. A., and Brown, C. F. G. (1950). Action of atropine on the cardiovascular system in normal persons. *Archives of Internal Medicine,* **86,** 898–907.

Pickering, G. W. (1968). *High Blood Pressure,* 2nd ed. J. and A. Churchill, London.

Pickering, T. G., Gribbin, B., Strange Petersen, E., Cunningham, D. J. C., and Sleight, P. (1972). Effects of autonomic blockade on the baroreflex in man at rest and during exercise. *Circulation Research,* **30,** 177–185.

Reid, J. L., Zivin, J. A., and Kopin, I. J. (1975). Central and peripheral adrenergic mechanisms in the development of deoxycorticosterone-saline hypertension in rats. *Circulation Research,* **37,** 569–579.

Safar, M. E., London, G. M., Weiss, Y. A., and Milliez, P. L. (1975). Vascular reactivity to norepinephrine and hemodynamic parameters in borderline hypertension. *American Heart Journal,* **89,** 480–486.

Smyth, H. S., Sleight, P., and Pickering, G. W. (1969). Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. *Circulation Research,* **24,** 109–121.

Takeshita, A., Tanaka, S., Kuroiwa, A., and Nakamura, M. (1975). Reduced baroreceptor sensitivity in borderline hypertension. *Circulation,* **51,** 738–742.

Yu, P. N. (1969). *Pulmonary Blood Volume in Health and Disease,* p. 74. Lea and Febiger, Philadelphia.

Warner, H. R., and Russell, R. O. (1969). Effects of combined sympathetic and vagal stimulation on heart rate in the dog. *Circulation Research,* **24,** 567–573.

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Left ventricular apical thin point

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The wall thickness of the apex of the left ventricle has been measured at its thinnest point in 60 adult hearts at necropsy. This measured 2 mm or less in 97 per cent of them and 1 mm or less in 67 per cent.

Some types of sutureless epicardial pacemaker electrode are anchored into the ventricular myocardium by a corkscrew 6 mm long by 4 mm diameter (Naclerio and Varriale, 1974). Recently a patient died from haemorrhage at the site of insertion into the left ventricle. At necropsy, the ventricular thickness at the apical site of insertion was 4 mm (Vecht *et al.*, 1976). The first object of the present study was to find out how often the adult left ventricle is less than 6 mm at its apical thin point.

Imaging of the myocardium using Thallium-201 has recently been introduced as a clinical investigation. With this technique defects at the apex of the left ventricle are common in normal hearts and have been attributed to local anatomical thinness of the myocardium (Cook *et al.*, 1976). The second object of our study was to find out whether this thin point exists.

Methods

The 60 hearts were all from adults varying in age from 34 to 87, with a mean age of 68 years. Thirty-seven per cent were from women.

HEART APICES

These were obtained at necropsy. Any heart which showed evidence of local disease was excluded from the series. In the rest the apex was amputated about 3 cm from its tip and fixed in 10 per cent buffered formol saline. Each specimen comprised the apex and part of each ventricular free wall together with the distal part of the septum.

MEASUREMENTS

The height of the amputated apex was measured, as was the minimum left ventricular wall thickness at the level of amputation. The left ventricular myocardium was cut into sagittal slices at 5 mm intervals. The right ventricular myocardium was then cut into coronal slices at 5 mm intervals. Each slice of the left ventricle was inspected and at its thinnest point the thickness of the muscle and of the overlying epicardial fat were measured. This sometimes required bisection of the relevant 5 mm slice, as the thinnest point was always very small. The thickness of the left ventricular wall was then measured in the adjacent slices (i.e. 5 mm to each side of the thin point). The thickness of muscle and fat in the right ventricle was also measured at its thinnest point which was often not at the apex.

All measurements are expressed as mean ± 1 standard deviation.

Results

LEFT VENTRICLE

Myocardium

The architecture of the apex of the left ventricle was remarkably constant. At the apex itself there was always one point where the myocardial thickness was 3 mm or less. The individual measurements are shown in Fig. 1a. In the whole series the mean thickness of the muscle at its apical thin point was 1·3 ± 0·7 mm. In some hearts the thin point measured less than 1 mm. An example of such a slice is shown in Fig. 2, and a photomicrograph shown in Fig. 3 shows how few strands of muscle separate endocardium from epicardial fat. In 2 out of the 60 hearts examined there were 2 apical thin points.

Fig. 1 also shows that the left ventricular myocardial thickness increased rapidly on each side of the apical thin point, so that when measured 5 mm away on one side the myocardial thickness was already 3·7 ± 2·3 mm on the thinner side (Fig. 1b) and 7·9 ± 6·3 mm on the thicker side (Fig. 1c). In the whole series the line of amputation

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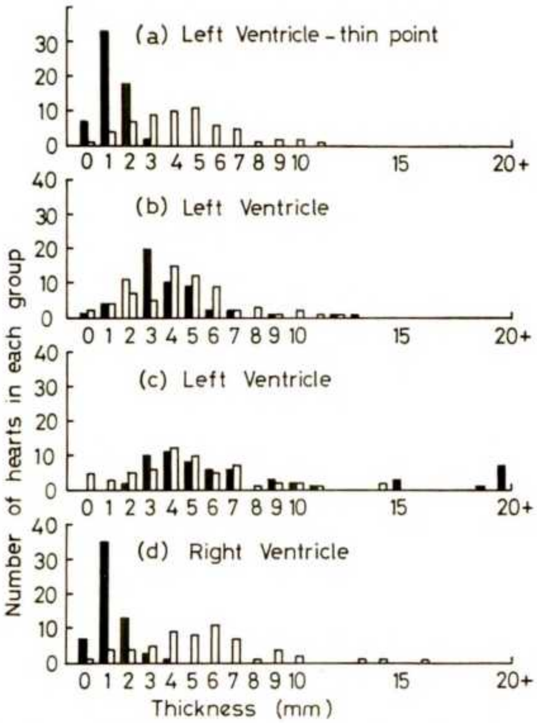

Fig. 1 *Histogram shows the thickness of muscle and fat in the ventricles of 60 hearts at necropsy. Solid columns—muscle; open columns—epicardial fat. A measured thickness of less than 0·5 mm is recorded as 0 mm. (a) Left ventricular thickness of muscle and fat at apical thin point; (b) Thickness of thinner 5 mm slice of left ventricular wall adjacent to apical thin point; (c) Thickness of the 5 mm slice of left ventricular wall on the other side of the apical thin point; (d) Least thickness of right ventricle. The position of measurement varied in different samples.*

was 29·0 ± 6·8 mm from the apical thin point and here the wall thickness was 14·0 ± 3·5 mm.

Epicardial fat

Fig. 1a, b, and c also show the thickness of the fat overlying the myocardium at the apex. This measured between 4·5 and 4·7 mm and is well illustrated in Fig. 2. At the apical thin point the epicardial fat was usually more than three times the thickness of the myocardium.

RIGHT VENTRICLE

In the right ventricle the architecture of the apex was different from that on the left side. The lumen was more convex and there was no single apical thin point. Instead there were several points

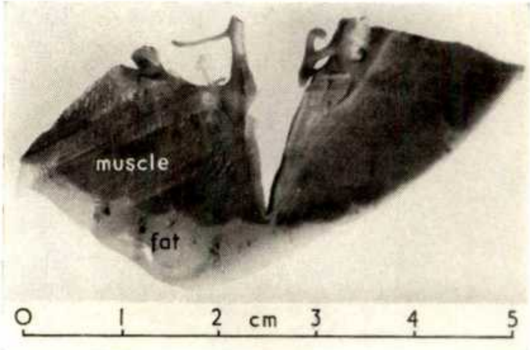

Fig. 2 *Sagittal slice of myocardium from the apex of the left ventricle of a 755 g heart. The piece has been arranged so as to display the apical thin point at which the endocardium comes to within 1 mm of the epicardial fat.*

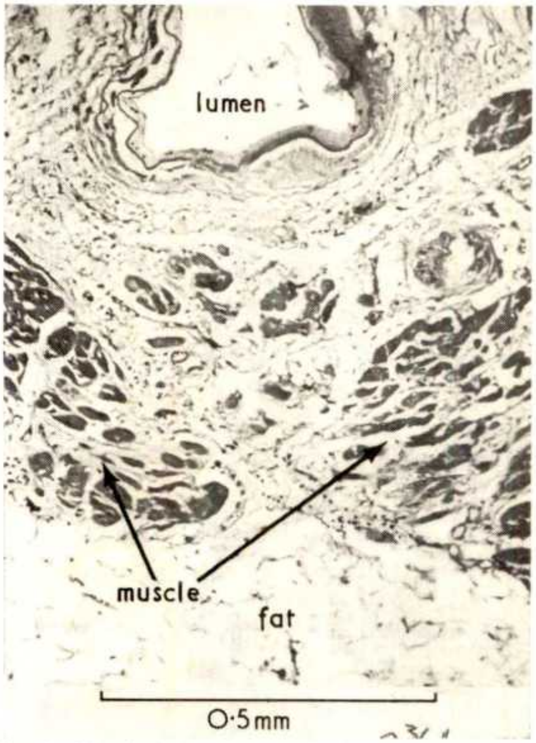

Fig. 3 *Histological section of apical thin point of the left ventricle of a 270 g heart (haematoxylin and eosin. ×110). Note the paucity of muscle between lumen and epicardial fat.*

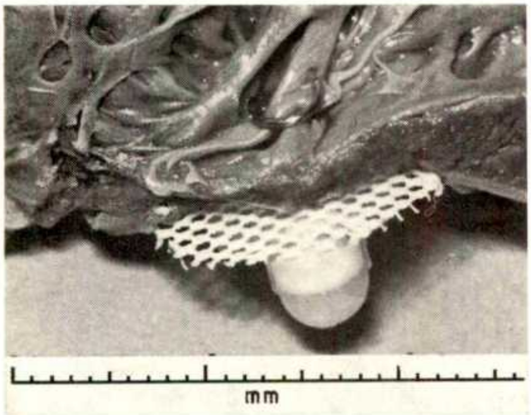

Fig. 4 *Epicardial corkscrew electrode inserted into the apex of a left ventricle at necropsy. The apex has been opened to show complete penetration of the corkscrew into the lumen.*

of equal thinness between trabeculations of the muscle. The individual dimensions are shown in Fig. 1d together with those of the overlying epicardial fat.

Comparison of Fig. 1a and d shows that the minimum myocardial thickness of the right ventricle of $1{\cdot}3 \pm 0{\cdot}8$ mm was very similar to that at the apex on the left side, and that the pad of overlying fat was similar in both regions.

PACEMAKER INSERTION

In order to assess how far a 6 mm corkscrew epicardial pacemaker electrode would penetrate when inserted, a corkscrew electrode (Model 6917, Medtronic Inc., Minn., U.S.A.) was screwed the recommended 3 turns into an unfixed fresh left ventricular apex at necropsy. Penetration into the lumen is illustrated in Fig. 4.

Discussion

The use of corkscrew epicardial pacing electrodes was first described in 1973 (Hunter *et al.,* 1973). About 30 000 have now been used, with few complications and only one reported fatal haemorrhage (Vecht *et al.,* 1976). The corkscrew is 6 mm long and 4 mm in diameter comprising an insulated region and a stimulating region (Naclerio and Varriale, 1974). Our experience with postmortem hearts showed that the recommended 3 turns were sufficient to insert the thread of the corkscrew the full 6 mm so that the Dacron netting guard came to lie against the epicardium. Recommendations for the site of implantation vary. Some authors suggest that the corkscrew be inserted as near to the apex of the ventricle as possible (O'Neill and Spagna, 1974). Failing this the anterior aspect of the right ventricle is the site of choice. In our series of measurements most hearts had one small point at the apex of the left ventricle at which the thickness of the myocardium was only 1 to 2 mm, sometimes less. The overlying epicardial fat was almost always thicker than this but provides no grip for a corkscrew. In view of this it is not surprising that it was easy to insert the pacemaker into a postmortem heart in such a way as to cause penetration into the lumen of the left ventricle. This result differs from that of a previous report in which penetration was never observed during a series of 25 insertions into right ventricular myocardium (Naclerio and Varriale, 1974), even though the thickness of the latter is usually less than 3 mm (Olsen, 1973; and Fig. 1d).

Clinically, many thousands of epicardial pacemakers have been inserted in this way and it seems likely that a proportion of these have penetrated the ventricular wall. The fact that there has been only one reported case of fatal haemorrhage means that the left ventricular apical thin point must be of sufficiently small area to allow adequate anchorage by the surrounding muscle. The finding in two hearts of double apical thin points in the left ventricle is more disconcerting in that this variation might allow the intervening piece of muscle to be pulled out by a corkscrew electrode screwed into both thin points. Because of this we suggest that the preferred site of insertion of this type of epicardial electrode should be away from the exact apex of the left ventricle.

The arrangement of the muscle at the left ventricular apex illustrated by these measurements carries implications about the way in which muscle at the apex contracts. It seems unlikely that the very thin strands of myocardial muscle at this site could withstand the pressure generated within that chamber during systole. More probably the whorled arrangement of the muscle fibres (Thane, 1892; Fox and Hutchins, 1972) allows the narrow funnel to close off at the onset of systole so that the thinnest point is protected from the high pressure generated at the peak of contraction. No such arrangement is found in the right ventricle where the convexity of the lumen allows transmission of the lower pressure to the thin areas at the apex.

These anatomical findings are also important for the correct interpretation of cardiac radionuclide studies. During Thallium-201 myocardial imaging there is an area of decreased activity of the apex of the left ventricle in about 50 per cent of normal hearts (Cook *et al.*, 1976). The postulate that this is the result of local anatomical thinning is here substantiated. In addition gated blood pool studies using Technetium 99m-labelled albumin confirm that as systole begins the left ventricular myocardium contracts in such a way as to constrict the apical region (J. W. B. Bradfield—personal observations).

In short, the impression of pathologists that the left ventricle is very thin at its apex, even in hypertrophied hearts, is confirmed by measurements. Appreciation of the presence of this left ventricular apical thin point is important (i) for the design and use of corkscrew epicardial pacemakers, (ii) for the interpretation of myocardial images produced by radionuclides, and (iii) for the understanding of muscle contraction at the apex of the left ventricle.

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References

Cook, D. J., Bailey, I., Strauss, H. W., Rouleau, J., Wagner, H. N., and Pitt, B. (1976). Thallium-201 for myocardial imaging: appearance of the normal heart. *Journal of Nuclear Medicine*, **17**, 583–589.

Fox, C. C., and Hutchins, G. M. (1972). The architecture of the human ventricular myocardium. *Johns Hopkins Medical Journal*, **130**, 289–299.

Hunter, S. W., Bolduc, L., Long, V., and Quattlebaum, F. W. (1973). A new myocardial pacemaker lead (sutureless). *Chest*, **63**, 430–433.

Naclerio, E. A., and Varriale, P. (1974). 'Screw-in' electrode. New method for permanent ventricular pacing. *New York State Journal of Medicine*, **74**, 2391–2395.

Olsen, E. G. J. (1973). *The Pathology of the Heart*. Intercontinental Medical Book Corp., New York.

O'Neill, J. E., and Spagna, P. M. (1974). *Implantation of the Model 6917 Sutureless Lead Wire. Subxiphoid and Infradiaphragmatic Approach.* Medtronic, Minneapolis.

Thane, G. D. (1892). In *Quain's Elements of Anatomy*, 10th ed., vol. 2, part 2. Longmans, Green, London.

Vecht, R. J., Fontaine, C. J., and Bradfield, J. W. B. (1976). Fatal outcome arising from use of a sutureless 'corkscrew' epicardial pacing electrode inserted into apex of left ventricle. *British Heart Journal*, **38**, 1359–1362.

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Atrioventricular reciprocal rhythm and chronic reciprocating tachycardia in a newborn infant with concealed Wolff-Parkinson-White syndrome

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A case of atrioventricular reciprocal rhythm and chronic reciprocating tachycardia in a newborn infant is presented. Electrophysiological studies suggest that these rhythm disturbances are related to the presence of a right-sided atrioventricular accessory pathway capable only of retrograde conduction (concealed Wolff-Parkinson-White syndrome). The technique of recording the sequence of atrial activation during the tachycardia is described and its clinical importance emphasised.

An impulse originating in the sinus node or in the atria may, in its course to the ventricles, retrogradely reactivate the atria. This phenomenon, when perpetuated, may produce a run of reciprocating tachycardia (Kistin, 1965). The presence of dual pathways or the development of functional longitudinal dissociation within the atrioventricular node is known to favour its occurrence (Mendez and Moe, 1966; Denes *et al.*, 1973). Experimental studies have shown that such a phenomenon can also occur in the sinus node (Han *et al.*, 1968) and in atrial tissue (Allessie *et al.*, 1973). An additional analogous situation is the existence of an accessory atrioventricular pathway in the Wolff-Parkinson-White syndrome which permits rapid conduction in a ventriculoatrial direction (Wolff, 1959; Roelandt and Van der Hauwaert, 1968). This paper relates the occurrence of atrioventricular reciprocal rhythm and chronic reciprocating tachycardia in a newborn infant with 'concealed' WPW syndrome in which an atrioventricular accessory pathway is capable only of retrograde conduction (Zipes *et al.*, 1974; Neuss *et al.*, 1975; Wellens and Durrer, 1975). The technique of recording the sequence of atrial activation during tachycardia is described and its clinical importance emphasised.

Case report

A 23-year-old black woman was diagnosed as having a breech position of the fetus at the 38th week of gestation. Simultaneously, fetal distress was clinically suspected because of the finding of a 'cardiac arrhythmia' on auscultation of the fetal heart sounds. Subsequently, a caesarian section was performed. The birthweight of the baby boy was 4024 g (7 lb 3 oz), and the baby appeared normal. However, frequent episodes of abrupt onset and termination of a tachycardia at a rate of 250/minute (Fig. 1) were noted immediately after birth. Since neither gross cardiac anomaly nor cardiac decompensation was present, the newborn was observed for 10 days and was discharged without any medication.

Two weeks later, the baby was admitted with a history of anorexia and vomiting of 4 days' duration. On admission, now 24 days old, the baby was afebrile, acyanotic, but pale and tachypnoeic, with a respiration rate of 80 per minute. Blood pressure was 70/40 mmHg in the arms and the apical heart rate was 250/minute and regular. No murmurs were audible. There were moist râles at both lung bases. The liver was palpable 3·5 cm below the right costal margin. Other findings were unremarkable. The chest x-ray film indicated slight cardiac enlargement and a moderate degree of pulmonary venous engorgement. Laboratory data and clinical observations indicated no evidence of thyroid dysfunction or myocarditis. On the electrocardiogram, there was right ventricular predominance compatible with the age, and the rhythm disturbance was the same as had been observed since birth (Fig. 1). The mechanism by which this rhythm disturbance occurred was interpreted as an

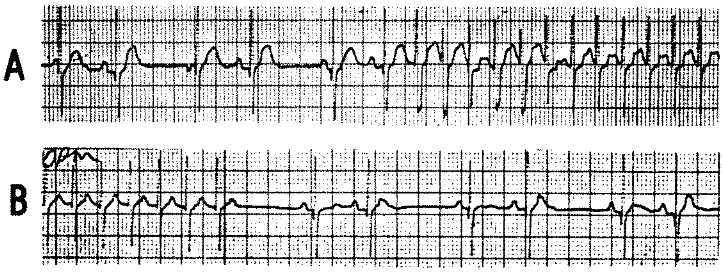

Fig. 1 *Abrupt onset and termination of tachycardia. The distorted T waves corresponding to the 2nd and 4th QRS complexes in the upper panel and the 9th, 11th, and 13th QRS complexes in the lower panel were interpreted as non-conducted 'premature atrial beats' with resetting of the cardiac cycle length. The tachycardia was considered as a form of 'ectopic atrial tachycardia'. Panels A and B were not continuous.*

'ectopic atrial tachycardia' and frequent 'non-conducted premature atrial beats'. The boy was given diuretic therapy and was accordingly digitalised (digoxin 0·14 mg I.V. in 24 hours followed by 0·09 mg orally per day). Intermittent episodes of the tachycardia persisted despite gradual increase in oral digoxin dosage (serum concentration up to 3·5 ng/ml). Digoxin was then discontinued and propranolol instituted (0·095 mg I.V. followed by 0·025 mg orally every 6 hours). The dosage of propranolol was also gradually increased but failed to control the arrhythmia. After discontinuance of propranolol for 2 days, cardiac catheterisation was performed in a post-absorptive basal state after pethidine and promethazine sedation. Only a patent foramen ovale was found.

ELECTROPHYSIOLOGY

After completion of the above study, a tripolar electrode catheter was introduced from the right femoral vein, and under fluoroscopy, positioned across the septal leaflet of the tricuspid valve to obtain His bundle electrograms. As usual, low septal right atrial activity was recorded from the same electrode catheter as well. Through the same femoral vein, an additional tetrapolar electrode catheter was placed in the atria for the purpose of recording atrial electrograms and pacing the corresponding atrium. During sinus rhythm, the PA, AH, and HV intervals were 25, 80 and 30 ms, respectively (Fig. 2). These values were normal for the age (Roberts and Olley, 1972). Of note, there were frequent P–QRS–P′ complexes interrupting the cardiac cycle. The electrocardiographic characteristics of these P–QRS–P′ complexes fulfilled the diagnostic criteria of a 'reciprocal rhythm' (Kistin, 1965; Roelandt and Van der Hauwert, 1968) in which the P′ waves were related to retrograde activation of the atria (the low septal right atrium in the vicinity of the atrioventricular node was activated 20 ms before the high right atrium) (Fig. 2). The question arises whether the P′ waves were not, in fact, premature beats from an atrioventricular nodal or low atrial focus. The

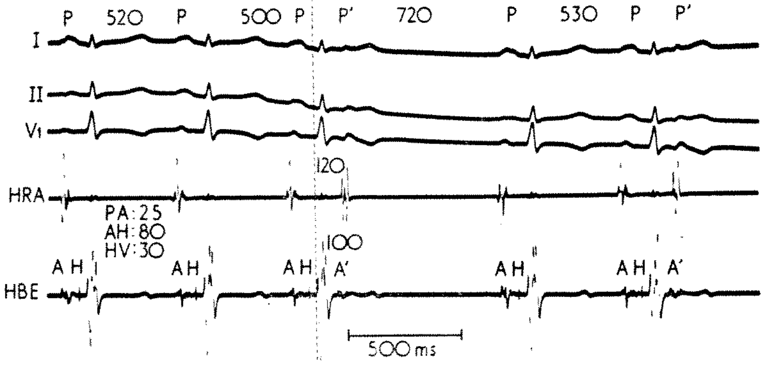

Fig. 2 *Atrial reciprocal rhythm. Initiation of atrial reciprocal (echo) beats, P–QRS–P′ complexes (the 3rd, and 5th QRS complexes), related to spontaneous shortening of the sinus cycle length. The PA, AH, and HV intervals (25, 80, and 30 ms, respectively) were normal for age. Using the onset of ventricular depolarisation (dash line) as a reference, the low septal right atrium (A′) in the His bundle electrocardiographic lead (HBE) was activated 20 ms before the high right atrium (HRA) during the P′ waves (V–LRA = 100 ms; V–HRA = 120 ms).*

following prominent features negate this possibility. First, the occurrence of P′ waves was invariably preceded by shortening of the sinus cycle length. As shown in Fig. 2, spontaneous shortening of the sinus cycle length from 520 to 500 and from 720 to 530 ms, respectively, induced a P′ wave. Secondly, high right atrial pacing at a cycle length of 500 ms with only minimal increase in AH conduction time (5 ms increment) constantly induced 1:1 reciprocal rhythm (P–QRS–P′ complex) (Fig. 3). Thirdly, the QRS–P′ interval was constant in every P–QRS–P′ complex. These selective links, i.e. cycle length dependency and constant QRS–P′ interval, would be too fortuitous for atrioventricular nodal or atrial premature beats to occur. Furthermore, the reciprocal rhythm, when perpetuated, initiated a run of reciprocating tachycardia with a rate of 250/minute (cycle length 240 ms) (Fig. 4A). During the tachycardia, the sequence of atrial activation was the same as those of P′ waves during the reciprocal rhythm—the low septal right atrium being activated 20 ms before the high right atrium. More than 20 spontaneous bouts of this tachycardia were observed during the study. Without exception, in each instance, a gradual decrease in the sinus cycle length was a requisite condition for initiating tachycardia.

In order to record the sequence of atrial activation for the localisation of the pathway of ventriculo-atrial conduction during the tachycardia (Gallagher *et al.*, 1975; Wellens and Durrer, 1975), the tetrapolar catheter was manipulated during the tachycardia. Through the interatrial communication, the electrode catheter was placed in the left atrium, and it was noted that the left atrium was activated 15 ms after the low septal right atrium in the vicinity of the atrioventricular node during the tachycardia (Fig. 4B). The electrode catheter was then positioned in the low lateral right atrium at its junction with the inferior vena cava to record the low lateral right atrial electrogram, and this revealed that low lateral right atrial activation preceded low septal right atrial activation by 20 ms during the tachycardia (Fig. 4C). Thus the sequence of retrograde atrial

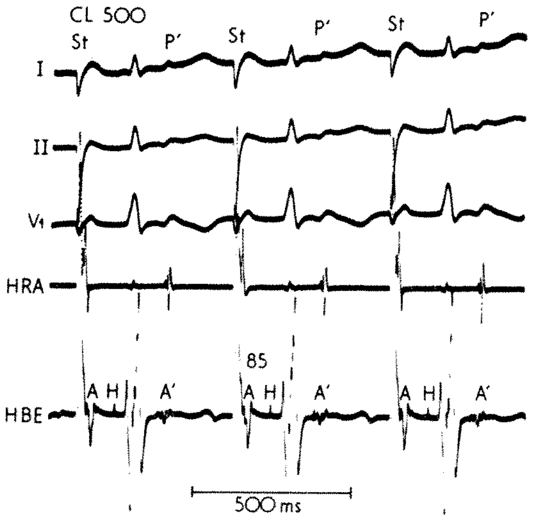

Fig. 3 *High right atrial (HRA) pacing at cycle length (CL) of 500 ms induced 1:1 reciprocal rhythm (P–QRS–P′ complex).*

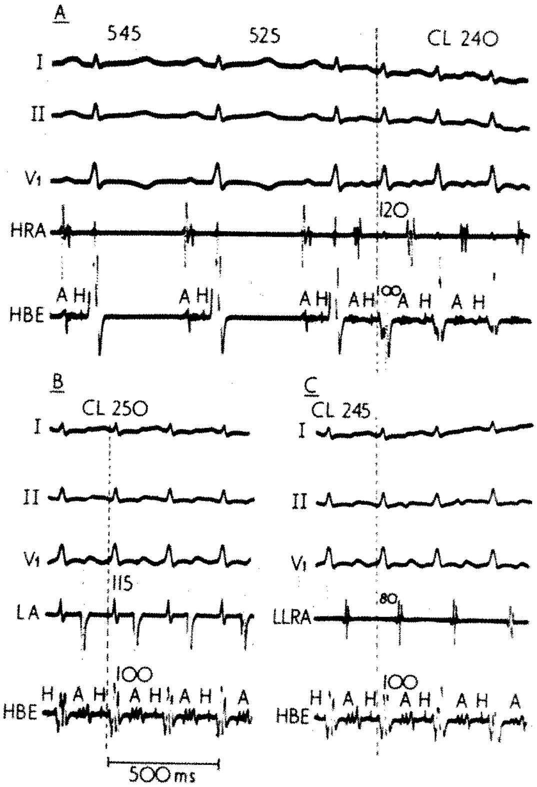

Fig. 4 *(A) Spontaneous onset of a run of reciprocating tachycardia preceded by a shortening of the sinus cycle length (CL) from 545 to 525 ms. During tachycardia (CL = 240 ms), the low septal right atrium (in HBE) is activated 20 ms before the high right atrium (HRA) (V–LRA = 100 ms; V–HRA = 120 ms). The dash line demarcates the onset of ventricular depolarisation.*
(B) During reciprocating tachycardia, the left atrium (LA) was activated 15 ms after the low septal right atrium (in HBE) (V–LA = 115 ms; V–LRA = 100 ms).
(C) During reciprocating tachycardia, the low lateral right atrium (LLRA) was activated 20 ms before the low septal right atrium (in HBE) (V–LLRA = 80 ms; V–LRA = 100 ms).

activation during tachycardia in this newborn started at low lateral right atrium, followed by low septal right atrium and then left atrium and high right atrium, suggesting the presence of a right-sided accessory atrioventricular pathway conducting in a ventriculoatrial direction (Gallagher *et al.*, 1975; Wellens and Durrer, 1975).

Electrical stimulation was performed in both atria. In no instance did ventricular pre-excitation ever become evident (anterograde conduction block in the accessory pathway, thus concealed on the surface electrocardiogram). Premature stimulation of either atrium could easily provoke and terminate a run of reciprocating tachycardia. Of note was the observation that late premature atrial beats which induced no or only minimal atrioventricular nodal conduction delay could trigger the onset of a run of tachycardia similar to what have been recently described in patients with 'concealed' WPW syndrome (Zipes *et al.*, 1974; Neuss *et al.*, 1975; Sung *et al.*, 1976).

Since the natural history of 'concealed' WPW syndrome is unknown at this young age, the newborn was discharged on a combination of digoxin (0·15 mg daily) and propranolol (7·5 mg every 6 hours) in addition to diuretic therapy. In a follow-up period of 6 months, episodes of atrioventricular reciprocal rhythm and reciprocating tachycardia persisted. However, the patient had remained clinically stable.

Discussion

That atrioventricular reciprocal rhythm and reciprocating tachycardia could be related to the existence of an accessory pathway capable only of retrograde conduction (concealed WPW syndrome) was first postulated by Codina-Altés and Pijoan de Beristain (1950) and later assumed by Eldridge (1958) and Schamroth (1960). The presentation of this case has thus confirmed this hypothesis. The following observations suggest that a right-sided accessory atrioventricular pathway (Kent bundle, type B) was responsible for the rhythm disturbances in this newborn infant.

(1) Abnormal sequence of retrograde atrial activation during the reciprocating tachycardia, i.e. the low lateral right atrium was activated 20, 35, and 40 ms before the low septal right atrium, the left atrium, and the high right atrium, respectively, indicating the presence of a right-sided accessory pathway conducting in a ventriculoatrial direction (Gallagher *et al.*, 1975; Wellens and Durrer, 1975).

(2) Anterograde conduction block in the accessory pathway, since ventricular pre-excitation was not evident during sinus rhythm, nor reciprocating tachycardia, and could not be induced by pacing either atrium.

As we have previously pointed out (Sung *et al.*, 1976), the initiation of a reciprocating tachycardia in patients with 'concealed' WPW syndrome may not require a triggering mechanism provided by a premature atrial beat owing to the presence of pre-existing anterograde unidirectional block in the accessory pathway. Under these circumstances, shortening of the sinus cycle length appears to be one of the factors favouring spontaneous onset of a reciprocating tachycardia. This is probably related to decrease in the refractory period of the atria and the accessory pathway, or a decrease in the depth of anterograde penetration of the accessory pathway, allowing the impulse to reactivate the atrium retrogradely; consequently, an atrioventricular reciprocal rhythm and/or a reciprocating tachycardia ensues. Spontaneous onset of a reciprocating tachycardia without an antecedent extrasystole can also be observed in patients with electrocardiographically manifest WPW syndrome (Krikler *et al.*, 1976) and in patients with dual atrioventricular nodal pathways (Coumel, 1975) when the sinus cycle length shortens to a critical point, at which anterograde unidirectional block develops in the accessory atrioventricular pathway and in one of the two intranodal pathways, respectively.

Management of chronic reciprocating tachycardia in patients with concealed WPW syndrome may present a therapeutic dilemma. Since anterograde unidirectional block is already present, the initiation of reciprocating tachycardia depends on the impulse arrival time at the ventricular end of the accessory pathway relative to the refractory periods of the corresponding atrium and the accessory pathway (Sung *et al.*, 1976). Digitalis and propranolol tend to prolong conduction time in the atrioventricular node which is a part of the tachycardia circuit. Therefore, both drugs can be used to prevent or interrupt the reciprocating tachycardia. However, prolongation of the atrioventricular nodal conduction time delays the impulse arrival at the ventricular end of the accessory pathway. Besides, digitalis may shorten the refractory periods of the atrium and the accessory pathway (Wellens and Durrer, 1973), and thus facilitate an onset of reciprocating tachycardia in these patients. Further studies on the efficacy of various pharmacological agents on the reciprocating tachycardias in patients with concealed WPW syndrome are needed.

In a long-term follow-up study on 62 infants and children with the WPW syndrome, Giardina *et al.* (1972) noted that the episodes of paroxysmal supraventricular tachycardia usually responded promptly to digitalis in the usual therapeutic dosage, and 'the prognosis into adult life' was quite good. Others (Lubbers *et al.*, 1972; Nadas *et al.*, 1952) had drawn similar conclusions. Nevertheless, these studies probably did not include patients with concealed WPW syndrome, since electrocardiographic evidence was the only criterion for inclusion. Thus, the true incidence of concealed WPW syndrome may be much greater than is generally realised. The report of this newborn with the concealed WPW syndrome which probably began in fetal life, and later, the follow-up will certainly add to the knowledge of the natural history of patients with the WPW syndrome.

References

Allessie, M. A., Bonke, F. I. M., and Schopman, F. J. G. (1973). Circus movement in rabbit atrial muscle as a mechanism of tachycardia. *Circulation Research,* **33,** 54–62.

Codina-Altés, J., and Pijoan de Beristain, C. (1950). Short paroxysms of tachycardia due to reciprocating rhythm. *American Heart Journal,* **39,** 436–443.

Coumel, P. (1975). Junctional reciprocating tachycardias. The permanent and paroxysmal forms of A-V nodal reciprocating tachycardias. *Journal of Electrocardiology,* **8,** 79–90.

Denes, P., Wu, D., Dhingra, R. C., Chuquimia, R., and Rosen, K. M. (1973). Demonstration of dual A-V nodal pathways in patients with paroxysmal supraventricular tachycardia. *Circulation,* **48,** 549–555.

Eldridge, F. L. (1958). Reciprocal beating of the atria. *American Heart Journal,* **55,** 469–475.

Gallagher, J. J., Gilbert, M., Svenson, R. H., Sealy, W. C., Kasell, J., and Wallace, A. G. (1975). Wolff-Parkinson-White syndrome. The problem, evaluation, and surgical correction. *Circulation,* **51,** 767–785.

Giardina, A. C. V., Ehlers, K. H., and Engle, M. A. (1972). Wolff-Parkinson-White syndrome in infants and children. A long term follow-up study. *British Heart Journal,* **34,** 839–846.

Han, J., Malozzi, A. M., and Moe, G. K. (1968). Sino-atrial reciprocation in the isolated rabbit heart. *Circulation Research,* **22,** 355–362.

Kistin, A. D. (1965). Atrial reciprocal rhythm. *Circulation,* **32,** 687–707.

Krikler, D., Curry, P., Attuel, P., and Coumel, P. (1976). 'Incessant' tachycardias in Wolff-Parkinson-White syndrome. *British Heart Journal,* **38,** 885–896.

Lubbers, W., Wellens, H. J. J., and Losekoot, G. (1972). Supraventricular tachycardia in infancy and childhood. *Bulletin of the Association of European Pediatric Cardiology,* **8,** 50–58.

Mendez, C., and Moe, G. K. (1966). Demonstration of a dual A–V nodal conduction system in the isolated rabbit heart. *Circulation Research,* **19,** 378–393.

Nadas, A. S., Daeschner, C. W., Roth, A., and Blumenthal, S. L. (1952). Paroxysmal tachycardia in infants. Study of 41 cases. *Pediatrics,* **9,** 167–181.

Neuss, H., Schlepper, M., and Thormann, J. (1975). Analysis of re-entry mechanisms in three patients with concealed Wolff-Parkinson-White syndrome. *Circulation,* **51,** 75–81.

Roberts, N. K., and Olley, P. M. (1972). His bundle recordings in children with normal hearts and congenital heart disease. *Circulation,* **45,** 295–299.

Roelandt, J., and Van der Hauwaert, L. G. (1968). Atrial reciprocal rhythm and reciprocating tachycardia in Wolff-Parkinson-White syndrome. *Circulation,* **38,** 64–72.

Schamroth, L. (1960). Reversed reciprocating paroxysmal tachycardia and its relationship to the Wolff-Parkinson-White syndrome. *American Heart Journal,* **59,** 506–517.

Sung, R. J., Castellanos, A., Gelband, H., and Myerburg, R. J. (1976). Mechanism of reciprocating tachycardia initiated during sinus rhythm in concealed Wolff-Parkinson-White syndrome. *Circulation,* **54,** 338–344.

Wellens, H. J. J., and Durrer, D. (1973). Effects of digitalis on A–V conduction and circus movement tachycardias in patients with Wolff-Parkinson-White syndrome. *Circulation,* **47,** 1229–1233.

Wellens, H. J. J., and Durrer, D. (1975). The role of an accessory atrioventricular pathway in reciprocal tachycardia. Observations in patients with and without the Wolff-Parkinson-White syndrome. *Circulation,* **52,** 58–72.

Wolff, L. (1959). Anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). *Circulation,* **19,** 14–27.

Zipes, D. P., DeJoseph, R. L., and Rothbaum, D. A. (1974). Unusual properties of accessory pathways. *Circulation,* **49,** 1200–1211.

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Primary thrombosis of pulmonary artery in a child with tetralogy of Fallot

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A 34-month-old child with tetralogy of Fallot developed an acute, primary thrombosis of the pulmonary trunk. A greatly increased haematocrit was most probably a predisposing factor. An unusual postmortem finding was the large number of extremely dilated myocardial capillaries. In a review of a series of 394 consecutive necropsy cases with many kinds of cardiac anomalies, there was only one case (a 28-year-old man) with occluding thrombus formation in the pulmonary artery. This case also belonged to the Fallot group but a subacute glomerulonephritis seemed to be the major cause of death.

Thrombosis of the pulmonary trunk or its two main branches is regarded as a rarity in children (Gootman *et al.*, 1964). The majority of the paediatric cases have been thought to be primary thromboses in contrast to the secondary thrombi superimposed upon a previous pulmonary embolus. Pulmonary arterial thrombosis in childhood has mainly been reported in connection with dehydration (Rauchfuss, 1859; Gunter, 1941; Ball *et al.*, 1956; Brunk, 1959), broncho-pulmonary infections (Robin, 1875; Gehrt, 1923), nephrosis treated with corticosteroids, chlorothiazide, or spironolactone (Gootman *et al.*, 1964; Symchych and Perrin, 1965; Rosenkranz and Weissenbacher, 1967; Levin, 1967; Habib, 1968) and congenital heart disease. We describe here an example of the last-mentioned type which had unusual features.

Case report

This 34-month-old boy was of a healthy family. During his first year of life he had frequent episodes of intense cyanosis and dyspnoea, particularly after crying. Later, there was a certain improvement with less obvious cyanosis. During a hospital stay a year before death, a diagnosis of tetralogy of Fallot was made; the haematocrit then was 59 per cent. It was decided to postpone surgery for one or two years.

During the following year, however, his cyanosis and dyspnoea became progressively worse. One day he suddenly collapsed and developed rapidly increasing dyspnoea and cyanosis. A few hours later, he lost consciousness. There were no convulsions or pareses. On admission to hospital shortly afterwards, he was deeply cyanotic, cold, and unconscious. Respiration was deep and the rate was slightly increased. There was only time for a few blood tests: haematocrit 82 per cent, *p*H 7·04, standard bicarbonate 10 mmol/l, and P_{CO_2} 39 mmHg. He was treated with oxygen, careful venesection, and digitalis without effect, and died 10 hours after the onset of the attack.

Necropsy

Length 85 cm, weight 14 kg. There was pronounced diffuse cyanosis, with some foamy, blood-tinged fluid in the nostrils.

The lungs were dark and congested without signs of infarction or pneumonia. Microscopically, the dominant feature was a generalised occlusion, particularly of the minor vessels, caused by massive aggregates of conglutinated erythrocytes (Fig. 1), some of them more or less hyalinised. There were scattered small deposits of intravascular fibrin, and many of the red cell aggregates were partly coated by fibrin positive material (the Martius-scarlet-blue stain). Fibrin was not seen in the vessel walls.

The heart was enlarged (weight 105 g). The right ventricle was dilated and greatly hypertrophied. There was a diffuse subepicardial extravasation of blood. The aortic arch was moderately dilated and located on the left side. The ductus arteriosus was

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unidentifiable. The cardiac anomaly was a typical tetralogy of Fallot with slightly hypoplastic pulmonary arteries and pronounced infundibular stenosis of the right ventricle. The entire stem of the pulmonary artery was completely occluded by an adherent, apparently fresh thrombus which extended 3 mm into both main arteries (Fig. 2). The microscopical picture of the right ventricular myocardium was dominated by a remarkably large number of enormously dilated capillaries crammed with erythrocytes, but without the typical red cell aggregates as seen in the lungs (Fig. 3). Similar, but less pronounced, capillary changes were seen in the left ventricular myocardium. Microscopy also showed numerous minute myocardial haemorrhages and scattered degenerative changes (fragmentation, hyalinisation, loss of striation). Sections from the pulmonary artery showed fresh thrombus masses and some small, organised parietal thrombi.

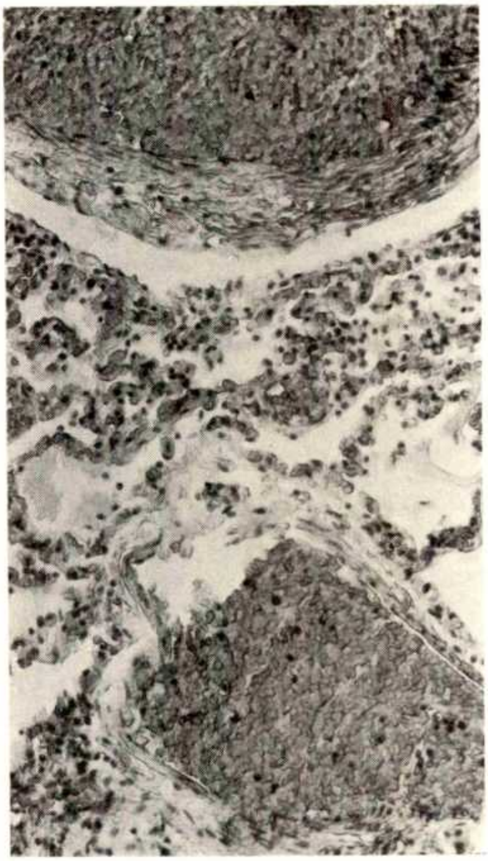

Fig. 1 *Section from lung showing the generalised occlusion of capillaries and minor vessels resulting from formation of massive aggregates of conglutinated erythrocytes.*

The liver was enlarged (weight 400 g) as a result of subacute congestive changes. The kidneys were also congested. Some small cortical vessels were occluded by conglutinated red cells, and a few of them contained minute amounts of fibrin. Similar changes were also seen in the spleen, pancreas, adrenals, thyroid gland, anterior lobe of the pituitary, and in numerous lymph nodes from various regions.

The cerebrospinal fluid was blood-tinged. Macroscopically, the brain was soft, oedematous and cyanotic with a remarkable congestion of the choroidal vessels. In the left lateral ventricle small clots were seen, probably caused by minor bleeding from the choroid plexus. Microscopy of the brain was not performed.

The large abdominal, thoracic, and pelvic veins showed no signs of thrombosis.

Discussion

Widespread and progressive thrombosis of the pulmonary vessels of *microscopical* size occurs frequently in patients with congenital pulmonary

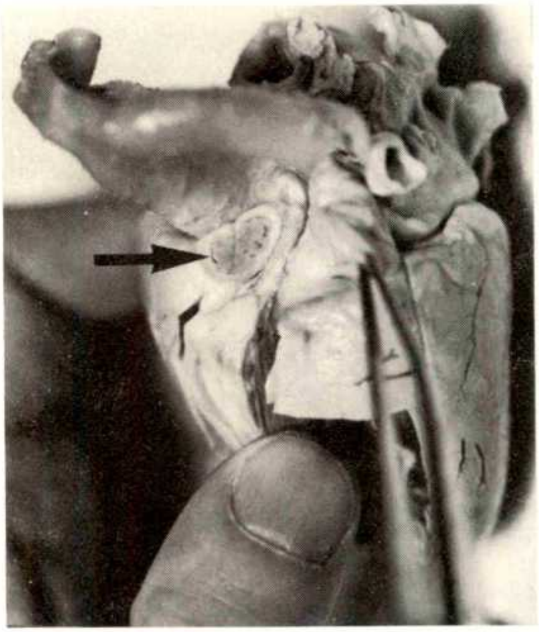

Fig. 2 *The base of the heart (formalin-fixed specimen). The pulmonary trunk is cut through. The arterial lumen is completely occluded by a fresh, adherent thrombus (arrow).*

artery stenosis (tetralogy of Fallot type). These thrombi occur independently of any operative procedure (Rich, 1948; Tosetti *et al.*, 1953; Best and Heath, 1958; Ferencz, 1960, 1964; Thomas, 1964). It has been suggested that the predisposing factors are the increased viscosity of the blood resulting from compensatory polycythaemia, and the reduced flow in the pulmonary vessels (Rich, 1948; Best and Heath, 1958). A remarkable tendency to recanalisation of the thrombi of the lungs, producing a characteristic appearance of the arteries with multiple lumina, has also been noted (Rich, 1948; Tosetti *et al.*, 1953). Severe microscopical pulmonary thromboses have been seen in patients who die during a cyanotic spell (Ferencz, 1960, 1964).

Massive *macroscopical* thrombosis involving both pulmonary arteries was seen in a 14-month-old infant with tetralogy of Fallot (Ring and Bakke, 1955). Similar changes were found in a 4½-year-old child with pulmonary stenosis and ventricular septal defect (Dickinson, 1897), in an 8-month-old infant with pulmonary atresia and terminal diarrhoea (Ball *et al.*, 1956), and in a 13-year-old patient with stenosis and subacute bacterial endarteritis of the pulmonary artery (Gordon and Perla, 1931). A ventricular septal defect was present in a 7-year-old patient, but in this case the possibility that trauma to the chest had played some part in the production of the defect must be considered (Harvey and Hogg, 1946).

Pulmonary arterial thrombosis has also been seen in a number of *adult* cases with cardiac anomalies, such as ventricular or atrial septal defects and persistent ductus arteriosus (Amos, 1958; Hudson, 1965).

In some cases, a more chronic thrombotic process of the pulmonary artery has been misinterpreted clinically as congenital heart disease, in children (Whipham, 1911) as well as in adults (Dimond and Jones, 1954; Breining, 1965).

In our case, an acute crisis apparently developed after a period of increasing severity of symptoms. It seems reasonable to relate the terminal events to the distinctly raised haematocrit value, which entails a considerable rise in blood viscosity

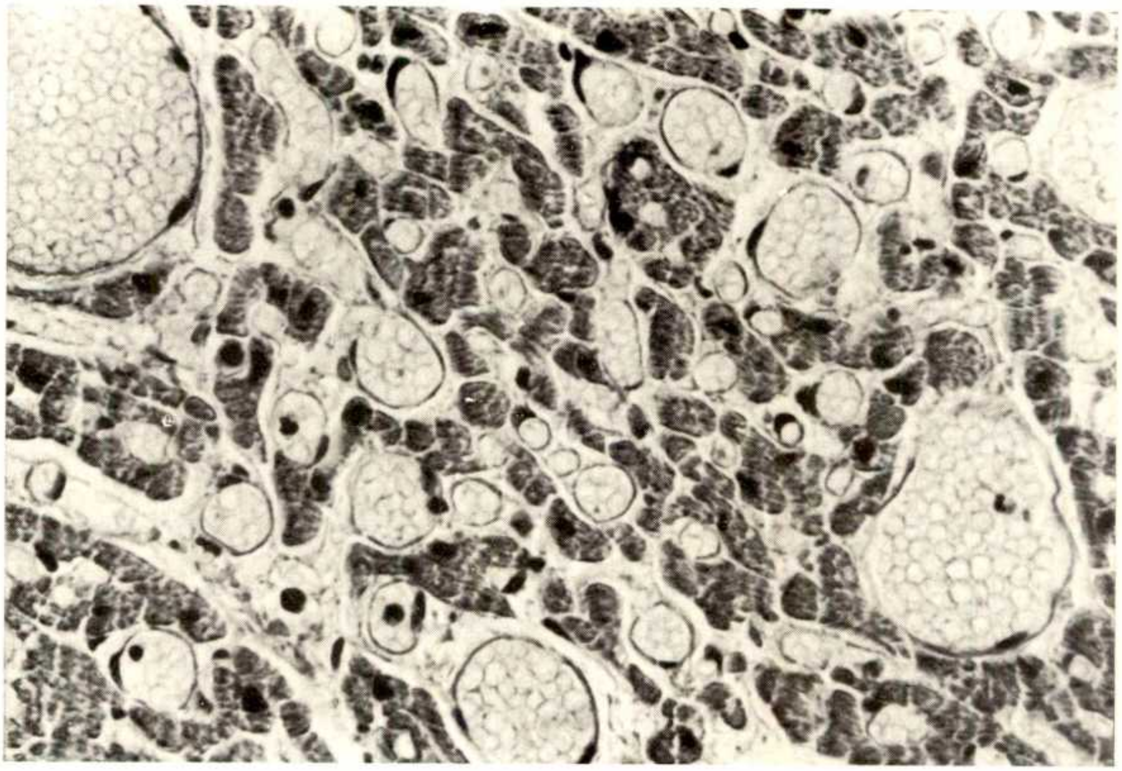

Fig. 3 *High power view of the right ventricular myocardium showing the large number of enormously dilated capillaries between the muscular elements.*

(Rudolph *et al.*, 1953). Harvey and Hogg (1946) have emphasised that one must suspect the possibility of pulmonary arterial thrombosis when a patient, who has congenital heart disease, develops a conspicuous increase in the severity of his symptoms. The onset may be acute with vomiting, perspiration, cyanosis, and collapse. Praecordial pain is usually a presenting symptom, but pain may be anywhere in the chest.

The postmortem demonstration of massive, widespread aggregates and intravascular fibrin deposits in our case aroused the suspicion of a terminal disseminated intravascular coagulation. Though we do not consider our findings as conclusive, we find it noteworthy that recent studies have suggested that a consumption coagulopathy may occur in certain cyanotic patients (Ihenacho *et al.*, 1973).

Analogous to some previous observations (Ring and Bakke, 1955; Ball *et al.*, 1956), the complete occlusion of the pulmonary stem in the present case did not imply any sign of pulmonary infarction.

A peculiar feature in our case was the large number of extremely dilated myocardial capillaries in the right ventricle, and to a lesser extent in the left ventricle. This close-meshed capillary network should possibly be considered to be a compensatory phenomenon (acute or chronic?) secondary to the heavy burden put on the myocardium.

Influenced by the study of the present case, we were interested to ascertain the incidence of congenital heart defects associated with primary thrombosis of the major pulmonary arteries. We have reviewed 394 consecutive necropsy cases with many kinds of cardiac anomalies presenting during the 20-year period 1946–65 at the University Institute of Pathology, Rikshospitalet, Oslo. The series included 38 cases with tetralogy of Fallot ranging from 2 months to 36 years of age. There was only one example of primary pulmonary arterial thrombosis which occurred in a case of Fallot's tetralogy. This patient was a 28-year-old man; one month before death he rapidly developed signs of serious renal insufficiency terminating with anuria. Necropsy revealed a narrow pulmonary trunk almost completely occluded by an adherent thrombus. Microscopically, the kidneys showed the picture of a subacute glomerulonephritis without any signs of the glomerular alterations described in cases of cyanotic heart disease (Spear, 1960; Spear and Vitsky, 1966). It is doubtful whether the pulmonary thrombus was of any importance in relation to the fatal outcome in this case.

Our study indicates that cardiac anomalies are only rarely associated with primary thrombotic occlusion of the major pulmonary arteries.

References

Amos, J. A. S. (1958). Thrombosis of the major pulmonary arteries. *British Medical Journal*, **2**, 659.

Ball, K., Goodwin, J. F., and Harrison, C. V. (1956). Massive thrombotic occlusion of the large pulmonary arteries. *Circulation*, **14**, 766.

Best, P. V., and Heath, D. (1958). Pulmonary thrombosis in cyanotic congenital heart disease without pulmonary hypertension. *Journal of Pathology and Bacteriology*, **75**, 281.

Breining, H. (1965). Zur Kenntnis der Pulmonalarterienthrombose. *Zeitschrift für Kreislaufforschung*, **54**, 254.

Brunck, H.-J. (1959). Primäre phlegmonöse Thrombarteriitis der A. pulmonalis bei einem Kleinkind. *Zentralblatt für allgemeine Pathologie und pathologische Anatomie*, **99**, 56.

Dickinson, L. (1897). Thrombosis of the pulmonary artery in a case of congenital stenosis of the orifice. *Transactions of the Pathological Society of London*, **48**, 57.

Dimond, E., and Jones, T. (1954). Pulmonary artery thrombosis simulating pulmonic valve stenosis with patent foramen ovale. *American Heart Journal*, **47**, 105.

Ferencz, C. (1960). The pulmonary vascular bed in tetralogy of Fallot. *Bulletin of the Johns Hopkins Hospital*, **106**, 81 and 100.

Ferencz, C. (1964). Pulmonary vascular changes in tetralogy of Fallot. *Diseases of the Chest*, **46**, 664.

Gehrt, D. (1923). Thrombose der Arteria pulmonalis im Kindesalter. *Zeitschrift für Kinderheilkunde*, **36**, 221.

Gootman, N., Gross, J., and Mensch, A. (1964). Pulmonary artery thrombosis. *Pediatrics*, **34**, 861.

Gordon, H., and Perla, D. (1931). Subacute bacterial endarteritis of pulmonary artery associated with patent ductus arteriosus and pulmonic stenosis. *American Journal of Diseases of Children*, **41**, 98.

Gunter, J. U. (1941). Thrombosis of the pulmonary artery in identical twins. *Archives of Pathology*, **31**, 211.

Habib, R., Courtecuisse, V., and Bodaghi, E. (1968). Thrombose des artères pulmonaires dans les syndromes néphrotiques de l'enfant. *Journal d'Urologie et de Néphrologie*, **74**, 349.

Harvey, E. B., and Hogg, P. (1946). Thrombosis of the pulmonary artery in children. *American Journal of Diseases of Children*, **71**, 67.

Hudson, R. E. B. (1965). *Cardiovascular Pathology*, pp. 1833–36. Edward Arnold, London.

Ihenacho, H. N. C., Breeze, G. R., Fletcher, D. J., and Stuart, J. (1973). Consumption coagulopathy in congenital heart-disease. *Lancet*, **1**, 231.

Levin, S. E., Zamit, R., and Schmaman, A. (1967). Thrombosis of the pulmonary arteries and the nephrotic syndrome. *British Medical Journal*, **1**, 153.

Rauchfuss, C. (1859). Ein Fall von Verstopfung der Lungenarterien eines 4 Wochen alten Kindes. *Virchows Archiv für pathologische Anatomie*, **17**, 474.

Rich, A. R. (1948). A hitherto unrecognised tendency to the development of widespread pulmonary vascular obstruction in patients with congenital pulmonary stenosis (tetralogy of Fallot). *Bulletin of the Johns Hopkins Hospital*, **82**, 389.

Ring, A., and Bakke, J. R. (1955). Chronic massive pulmonary artery thrombosis. *Annals of Internal Medicine*, **43**, 781.

Robin, A. (1875). Physiologie pathologique d'un cas de gangrène du poumon, avec oblitération de l'artère pulmonaire chez un enfant atteint de rougeole et de bronchopneumonie consécutive. *Progrès Médical*, **3**, 747.

Rosenkranz, A., and Weissenbacher, G. (1967). Thrombose der Lungenarterien als Komplikation des nephrotischen Syndroms. *Wiener klinische Wochenschrift*, **79**, 320.

Rudolph, A. M., Nadas, A. S. and Borges, W. H. (1953).

Hematologic adjustments to cyanotic congenital heart disease. *Pediatrics,* **11,** 454.

Spear, G. S. (1960). Glomerular alterations in cyanotic congenital heart disease. *Bulletin of the Johns Hopkins Hospital,* **106,** 347.

Spear, G. S., and Vitsky, B. H. (1966). Hyalinization of afferent and efferent glomerular arterioles in cyanotic congenital heart disease. *American Journal of Medicine,* **41,** 309.

Symchych, P., and Perrin, E. V. (1965). Thrombosis of the main pulmonary artery in nephrosis. *American Journal of Diseases of Children,* **110,** 636.

Thomas, M. A. (1964). Pulmonary vascular changes in pulmonary stenosis with and without ventricular septal defect. *British Heart Journal,* **26,** 655.

Tosetti, R., Actis Dato, A., and Angelino, P. F. (1953). Histo-pathologie des petits vaisseaux pulmonaires dans les sténoses congénitales de l'artère pulmonaire. *Archives des Maladies du Coeur et des Vaisseaux,* **46,** 780.

Whipham, T. (1911). A heart showing an infective polypoid thrombus in the pulmonary artery and extending into the right ventricle, mistaken for patent ductus arteriosus. *Proceedings of the Royal Society of Medicine,* **4 (part 1),** 199.

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Correspondence

British Heart Journal, 1977, **39**, 820

The watershed: a factor in coronary vein graft occlusion

Sir,

It was with some interest that we read the article by Dr. Simon Rees published in *British Heart Journal* (1976) **38,** 197–200. The suggestion offered by Dr. Rees that, because grafts to totally occluded arteries have a high patency rate, ligation of the coronary artery proximal to the anastomosis may be necessary to achieve the highest patency rate has not been borne out by our experience. As we feel that ligation may indeed be harmful, we would appreciate the opportunity to report our own results. This experience has been reported recently by us in an article entitled 'Patterns of patency of 596 vein grafts up to 7 years after aortocoronary bypass'. *Journal of Thoracic and Cardiovascular Surgery* (1977), **73,** 443.

In summary, we examined 596 vein grafts in 343 patients at a mean follow-up of 15·4 months. Overall graft patency was 84 per cent. Only 130 patients with 96 grafts were asymptomatic at the time of restudy and their graft patency was 91 per cent (178/196). Of the overall group of grafts, 95 had been attached to the distal segment of a totally occluded vessel and 78 were patent for a patency rate of 82 per cent. Our conclusion, therefore, was that graft patency was not significantly influenced by the presence of competitive flow. Indeed it has been our aim wherever possible to obtain bidirectional flow from the graft and this was achieved in 80 per cent of the grafts which were performed in this series.

It is not clear to us from the results presented why the results of the study of Dr. Rees should differ from ours, but we feel strongly that the suggestion that coronary arteries should be ligated proximally is incorrect and for this reason feel it important that our results be made known at this time.

Gerald M. Lawrie,
George C. Morris, Jr.,
William L. Winters,
Don W. Chapman,
Baylor College of Medicine,
Texas Medical Center,
Houston,
Texas 77030, U.S.A.

This letter was shown to Dr. Rees who comments as follows:

Sir,

The results of Lawrie *et al.* obviously suggest that graft occlusion is multifactorial, but I do not agree that the watershed has been shown not to be operative. Other factors nevertheless are obviously important including mainly the flow, and indeed the size of the grafted artery as quoted in my article.

Simon Rees,
5 Devonshire Place,
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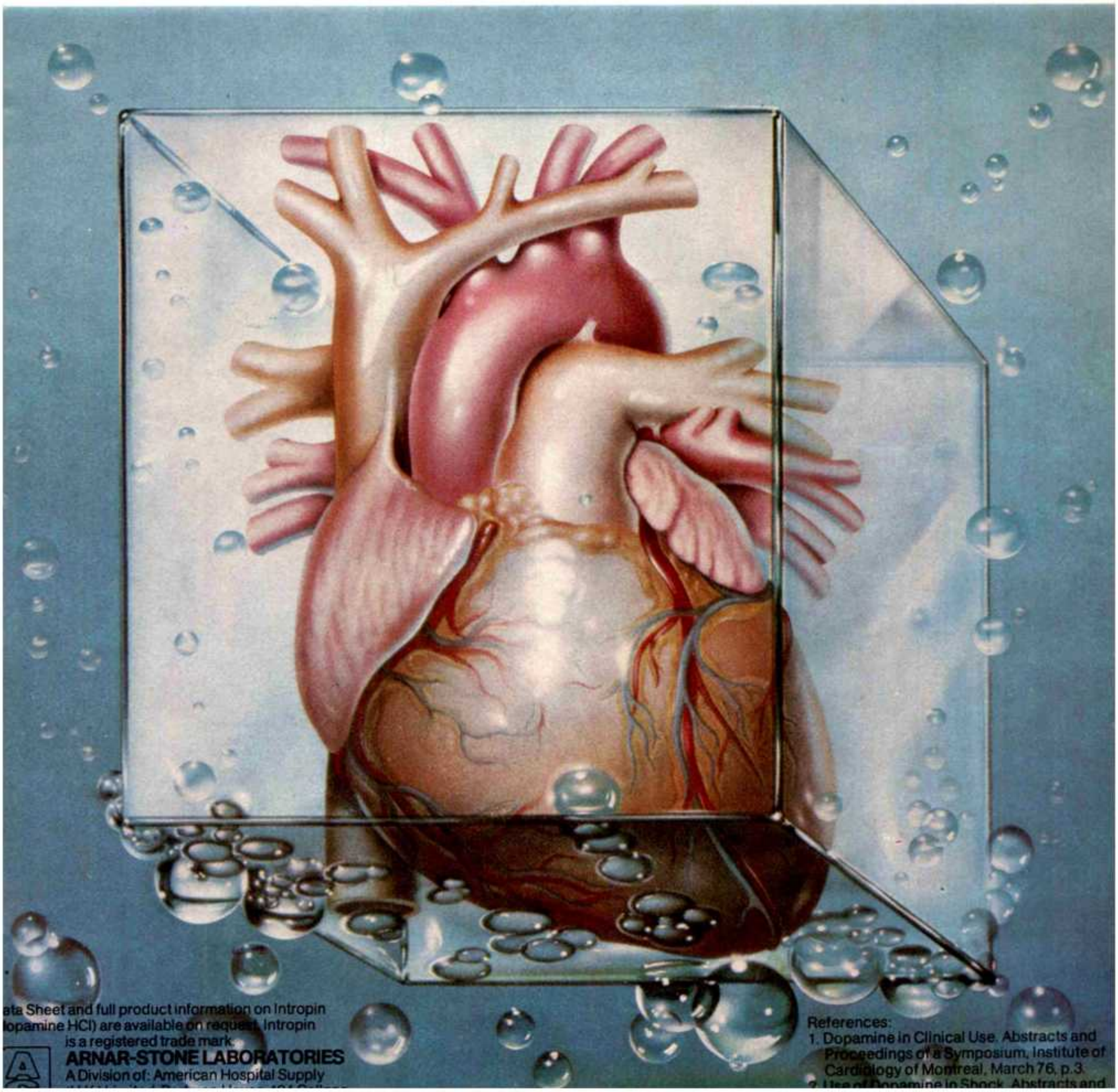

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1. Dopamine in Clinical Use. Abstracts and Proceedings of a Symposium, Institute of Cardiology of Montreal, March 76, p.3.
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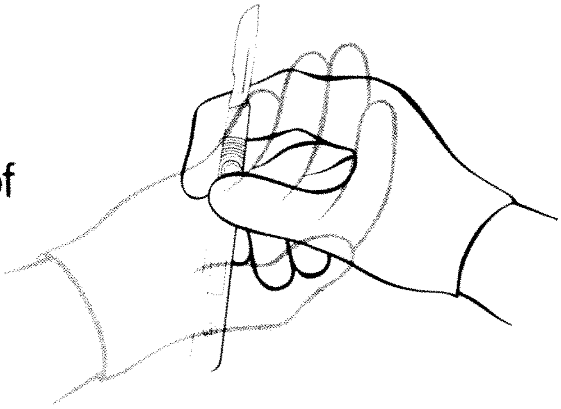

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A course on the theory and practice of echocardiography will be held in the Department of Cardiology, Newcastle General Hospital, from 5th—10th September, 1977. This is the autumn session of the bi-annual teaching course run jointly by Newcastle General Hospital and Harefield Hospital. It is intended for physicians, cardiologists, radiologists and senior technicians who have some experience of practical echocardiography, and deals with all the applications of the technique in acquired and congenital heart disease.

The co-chairmen are Dr. Ronald Pridie and Dr. Stewart Hunter and speakers will include Dr. Robert Anderson and Dr. Derek Gibson from the Brompton Hospital. A limited number of places are available and applications should be directed to **Dr. S. Hunter, Department of Cardiology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE** (Tel. 0642 38811 ext. 221/222) by 15th August, 1977.

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1. Postgrad. Med. J., 51, 10, (1975)
2. Danish Med. Bull., 21, 63, (1974)
3. Clin. Pharm. Ther., 15, 141, (1974)
4. J. Int. Med. Res., 2, 314, (1974)
5. Brit. J. Clin. Prac., 28, 311, (1974)
6. Brit. J. Clin. Prac., 29, 7, (1975)
7. Postgrad. Med. J., 51, (Suppl. 6), 54, (1975)
8. Brit. J. Clin. Prac. 30, 11-14 (1976)
9. Leading Article, Brit. Med. J., 2, 521, (1975)
10. J. Int. Med. Res., 3, 241, (1975)
11. Postgrad. Med. J., 51, (Suppl. 6), 71, (1975)
12. Acta. Med. Scand., 193, 119, (1973)
13. J. Int. Med. Res., 3, 104, (1975)
14. J. Int. Med. Res., 4, 37-41 (1976)

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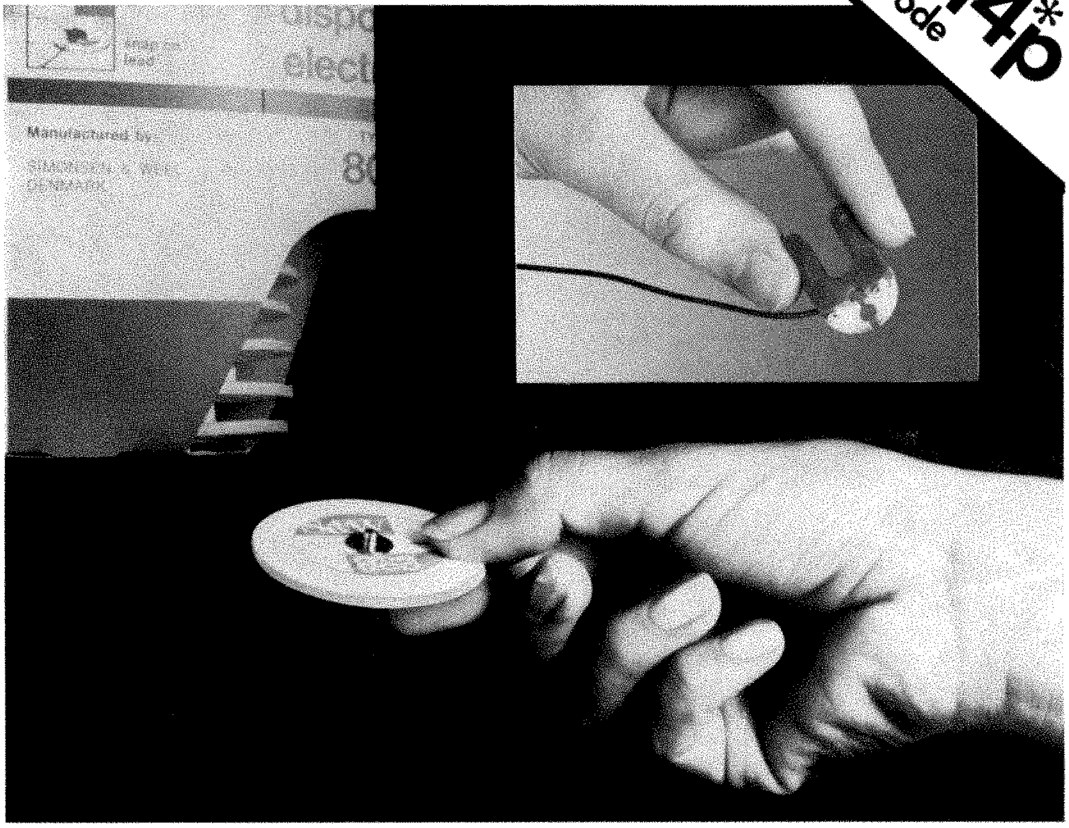

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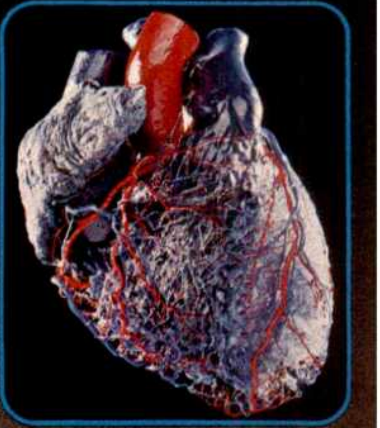

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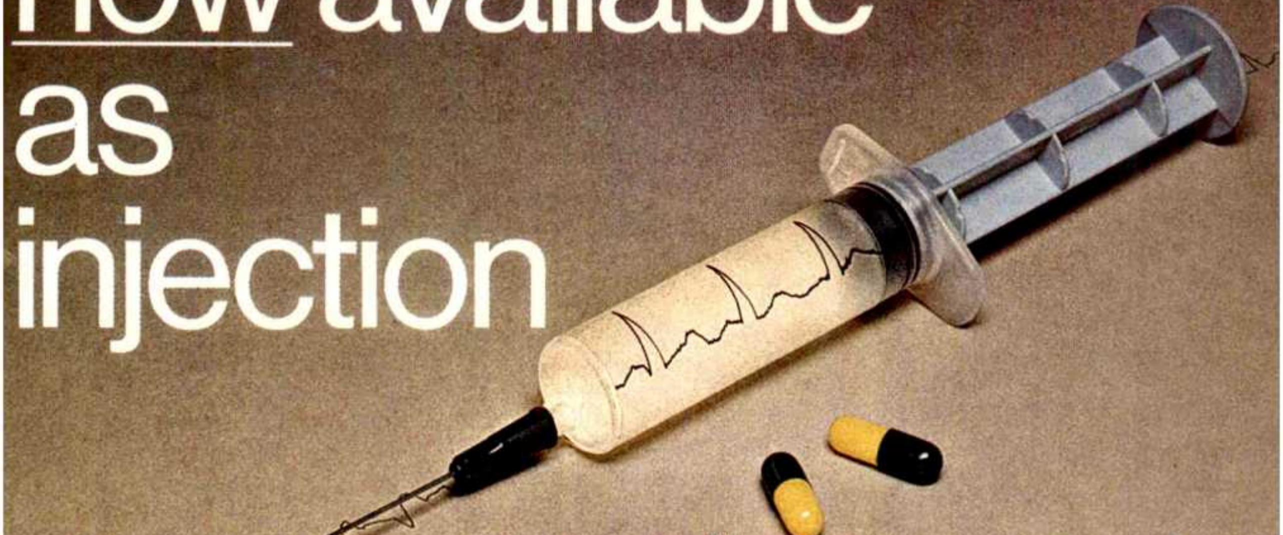

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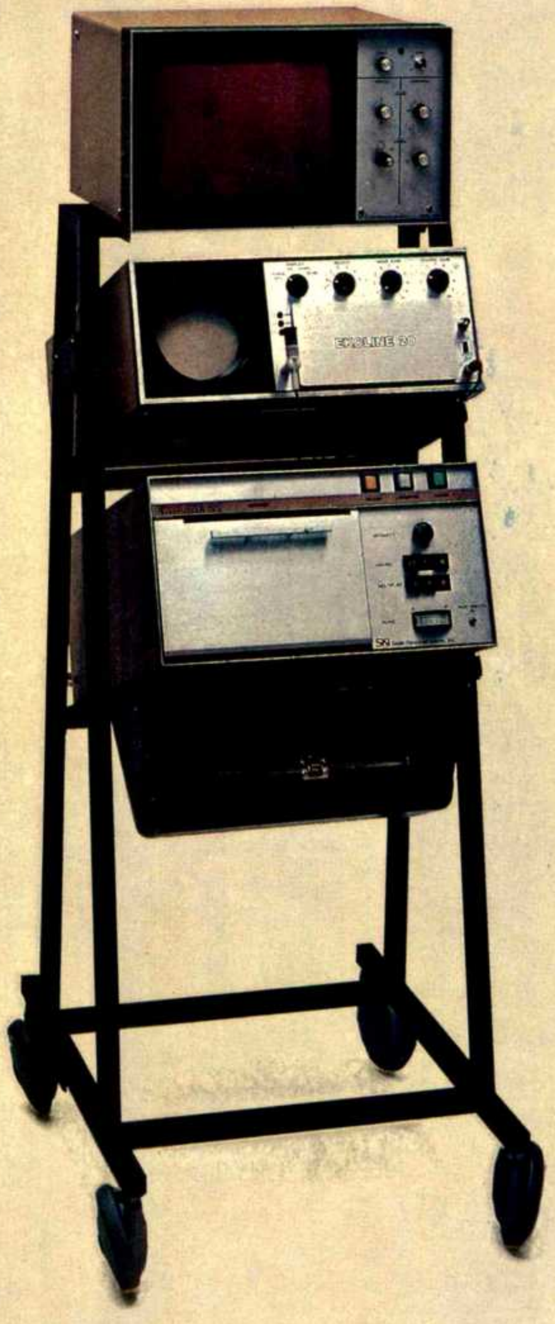

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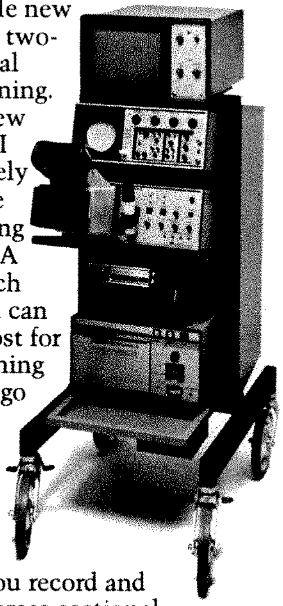

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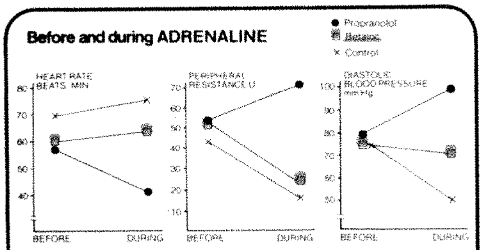

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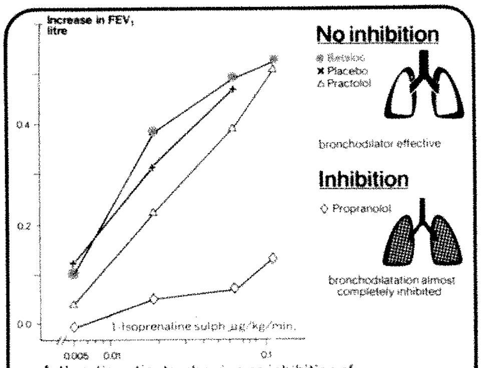

Asthmatic patients: showing no inhibition of isoprenaline effect by Betaloc, compared with almost complete inhibition by non-selective propranolol.

1 (1975) *Acta pharmacol et toxi* Suppl. V. 39-68 University of Gothenburg, Sweden.

2 Clinical Report (1975), University of Gothenburg, Sweden.

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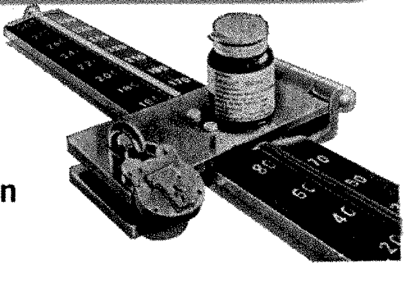

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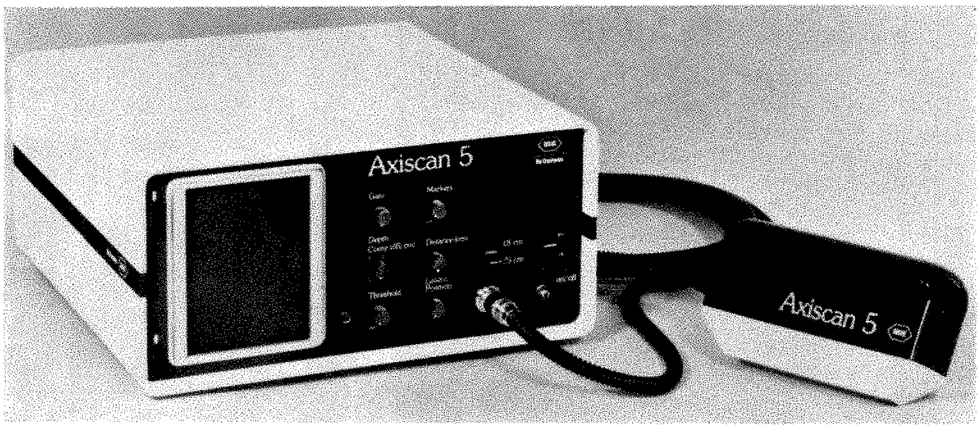

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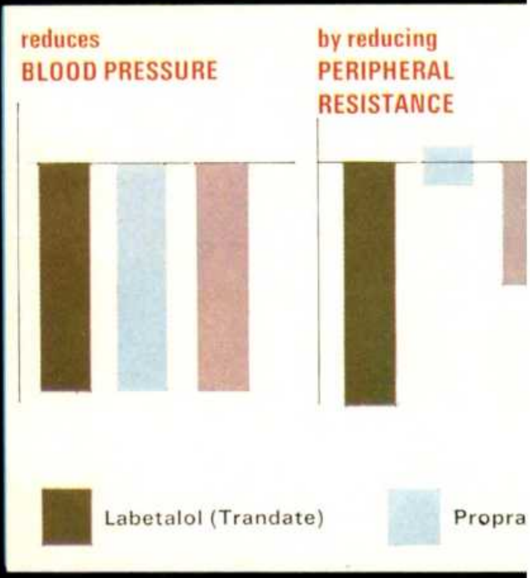

Diagram to illustrate the unique

"The major haemodynamic dysfunction in complicated essential hypertension is an incre peripheral vascular resistance associated unchanged cardiac output. The desirable ment, therefore, is to use drug treatments at reducing peripheral resistance. The

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HYPERTENSION

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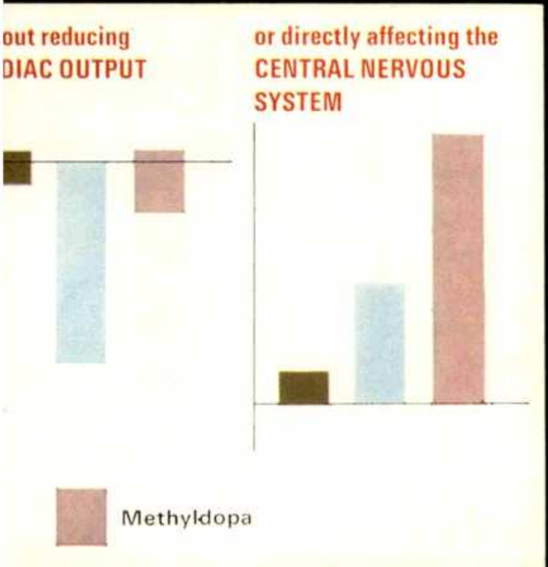

ction of Trandate in hypertension.

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Brit. J. clin. Pharmacol., 1976, **3** (Suppl.3), 757

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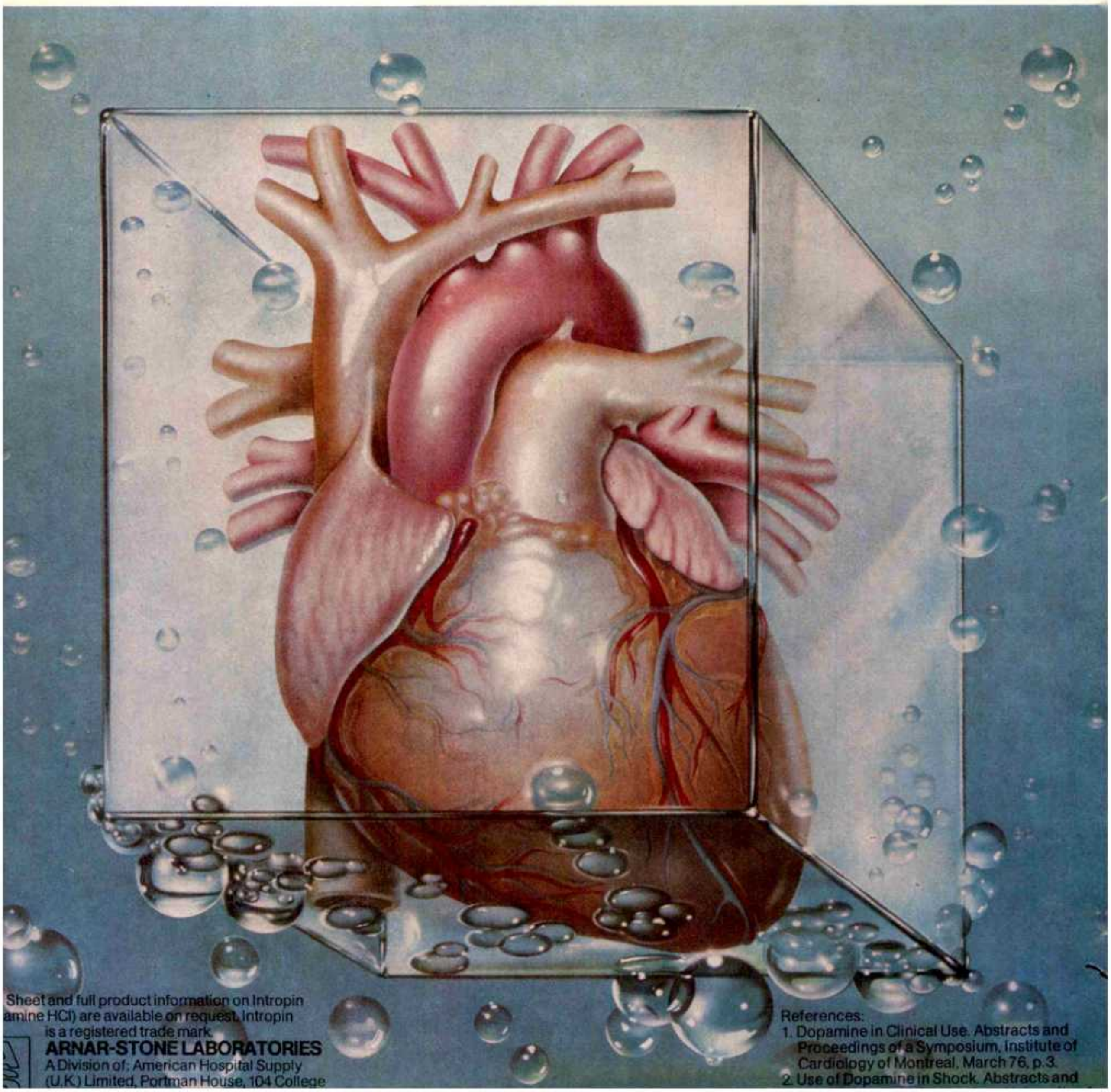

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2. Use of Dopamine in Shock. Abstracts and

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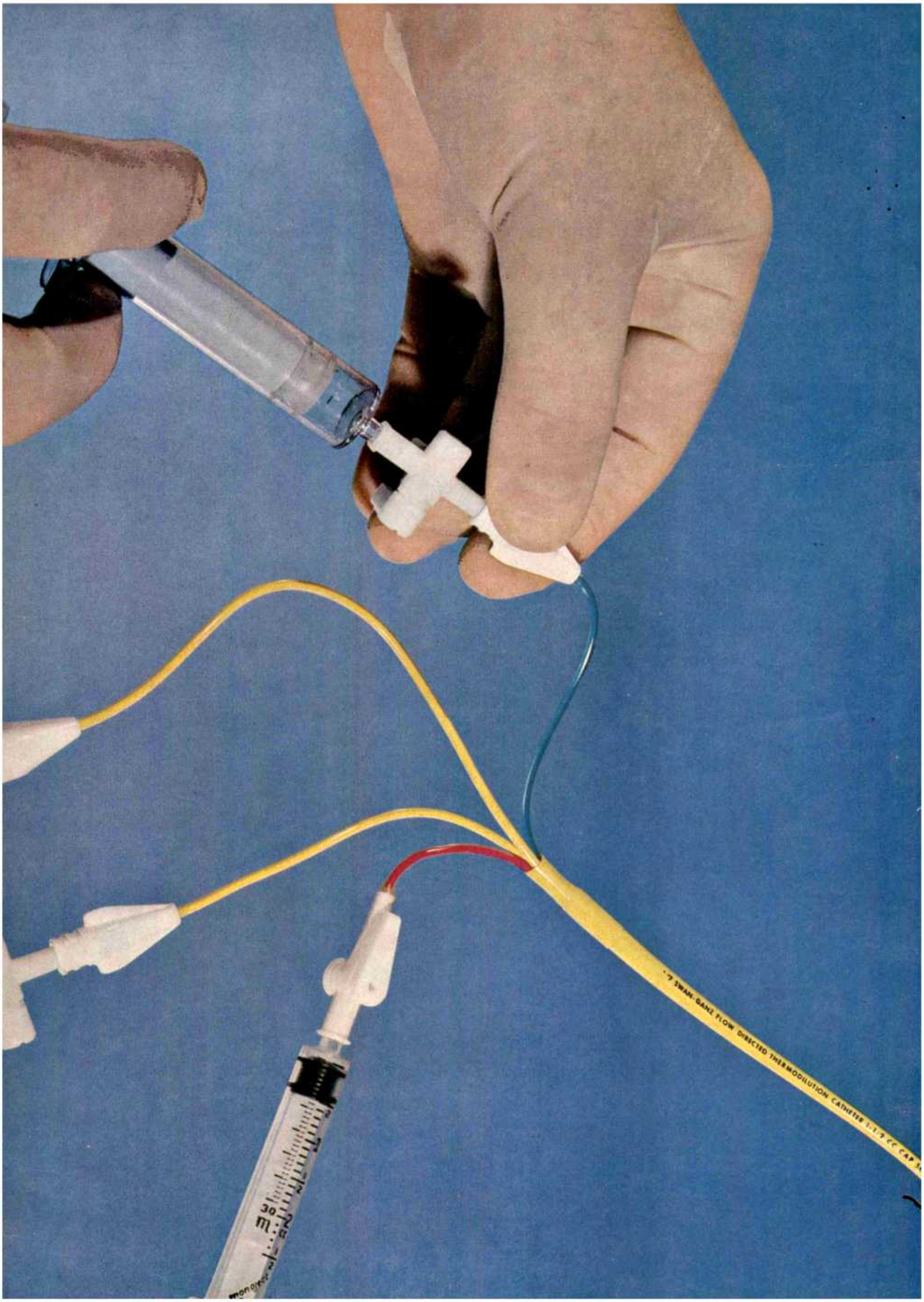
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4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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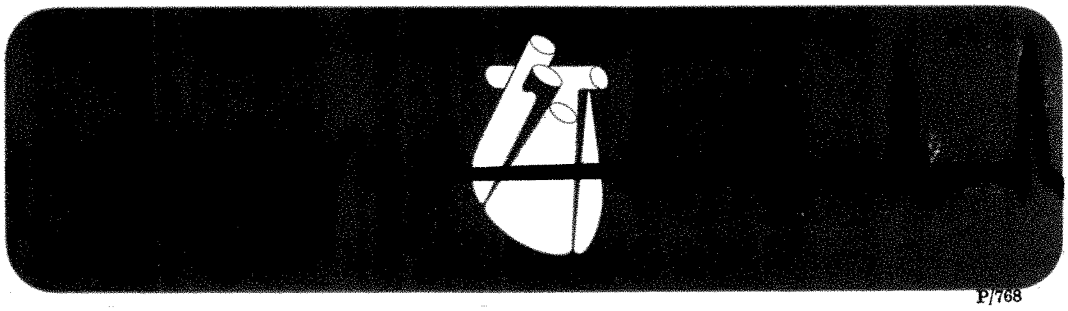

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Editorial

British Heart Journal, 1977, **39**, 821–824

Treating hypertension
The place of beta blockade

D. W. BARRITT[1] AND A. J. MARSHALL[1]

Hypertension is now usually discovered at routine examination or in patients who present with symptoms unrelated to the level of blood pressure. Investigation will rarely reveal a curable cause. Age, sex, and height of blood pressure usually decide whether medication should be started. These symptomless patients then face many years of swallowing tablets. Clearly, the ideal treatment regimen should lower blood pressure independently of posture, without inducing troublesome side-effects, and should be simple to prescribe and take. To the prescriber simplicity means confidence in potency and a dose range that is easy to adjust. To the patient it will seem a poor bargain to have to swallow a large number of tablets several times a day for a statistical chance of a longer life, especially if the tablets are not innocuous.

How closely does beta blockade approach this ideal?

POTENCY

All beta blocking drugs at present available have been shown to lower blood pressure (Morgan *et al.*, 1974; Davidson *et al.*, 1976). After recognising the hypotensive action of propranolol, Prichard and Gillam (1969) assessed its potency in a group of patients previously used in a trial to compare guanethidine, bethanidine, and methyldopa. They found propranolol to be of similar potency to the previously used drugs. Our own within-patient double-blind comparison of oxprenolol and methyldopa (Barritt *et al.*, 1976) showed virtually identical pressure falls with both drugs. Thomas and co-workers (1976) also compared methyldopa, oxprenolol, and spironolactone and found no significant differences between the hypotensive effects of the three agents.

Hydrochlorothiazide 50 mg daily was compared with timolol in a double-blind within-patient trial by Chalmers and co-workers (1976) and found to be slightly less potent. Petrie *et al.* (1975) have also shown that beta blockade causes a slightly greater fall in blood pressure than a thiazide diuretic in a trial which compared atenolol with 5 mg bendrofluazide daily.

We assessed oxprenolol used alone in 40 patients and found the range of fall in mean blood pressure was 0 to 40 mmHg (average fall 20 mmHg) (Barritt and Marshall, 1977). The maximum sustained fall in pressure in any patient was 62 mmHg systolic, and 42 mmHg diastolic (phase 5). These results are based on multiple measurements made before and during a prolonged period of treatment. It seems to be the case that when beta blocking drugs are compared with adrenergic neurone blocking drugs, methyldopa, or diuretics there is little to choose between them in terms of potency. Whichever agent is used, there will be a good fall in blood pressure in some patients and little in others. This is the trial and error element in the treatment of each hypertensive patient.

DOSE RANGE, ASSESSMENT OF RESPONSE, AND FREQUENCY OF ADMINISTRATION

Beta-blockade was slow to gain popularity partly because it was first suggested that the range of dosage with propranolol and oxprenolol was wide, and that the full effect might take as long as two months to be evident. It was disappointing to find that as the dose was slowly increased little further was achieved. Recent investigations leave little doubt that the effective dose range is in fact relatively narrow with most beta blocking agents, and that their full effect is known in as little as two weeks (Galloway *et al.*, 1976; Barritt and Marshall, 1977; Marshall *et al.*, 1977b).

It can now be predicted with confidence that, if a group of hypertensive patients is given propranolol or oxprenolol in a dose of 80 or 160 mg twice daily or atenolol 100 mg once daily, the average fall in mean blood pressure will be 20 mmHg and the range 0 to 40 mmHg. The result of treatment will be evident at the first out-patient visit. Though the plasma half-lives of these drugs suggested that they would need to be given three times daily, it is clear that the effect on heart rate, and especially blood pressure, may last 24 hours or more. The evidence that atenolol is as effective when given once daily as in divided doses appears conclusive (Woolfson and Knapp, 1976; Marshall *et al.*, 1977b). The same may well be true of propranolol and other beta blocking drugs (Wilson *et al.*, 1976). Beta blockade can be used as a simple once daily regimen for hypertension, and its effect fully assessed within two weeks.

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[1] Bristol Royal Infirmary.

SIDE-EFFECTS

Postural hypotension is exceptional with beta blockade, as is impairment of sexual performance or mental slowing, which are the major disadvantages of other current therapy. Used carefully in selected patients, side-effects are few. Nevertheless, beta-blockade invariably lowers cardiac output and is, therefore, quite unsuitable for patients with left ventricular failure. Though some beta blocking agents appear to have little effect on airways resistance, it seems wise to regard a history of wheezing as a contraindication to their use. The only common and undisputed side-effect of beta blockade is the development of cold hands and feet. When the specific question is asked, over one-quarter of patients taking beta blocking drugs admit to the development of cold hands and feet (Marshall *et al.*, 1976). Cold extremities are associated with absence of foot pulses and it is our practice to look for symptoms and signs of peripheral vascular disease, and if these are present to avoid beta blockade or use it with caution. Propranolol and atenolol commonly produce resting heart rates of 50 beats a minute. This is a good guide to the physician that the tablets have been taken, but bradycardia is not usually associated with symptoms unless the patient also has sinoatrial disease. Beta blockade is best avoided in insulin-dependent diabetics. Not only may the treatment mask the symptoms and signs of hypoglycaemic attacks, but may also help to induce hypoglycaemia by inhibiting hepatic gluconeogenesis.

No discussion of long-term treatment with beta-blockade can ignore the emergence of the practolol syndrome. All who prescribe these agents must be aware of its severity (Marshall *et al.*, 1977a). The use of beta blocking agents in therapeutics is an example of the oscillations in the popularity of a new drug, as described by Lawrence (1966). Initial interest was small, but through the persistent work of Prichard and his colleagues, they became acceptable antiarrhythmic and hypotensive agents. Within a few years they were widely prescribed and claimed to be the best treatment for diseases varying from schizophrenia to anxiety, thyrotoxicosis, and hypertrophic obstructive cardiomyopathy. Rashes, eye disease, and most important life-threatening peritoniteal fibrosis leading to progressive intestinal obstruction, associated with practolol therapy, have justly made many physicians hesitant to use long-term beta-blockade. Such adverse reactions in the few have undoubtedly to be balanced against the unquestioned benefits to the many patients who have been treated. Each new beta blocking agent will need to be monitored with the utmost vigilance, but it does now seem certain that no sinister syndrome will follow the use of propranolol or oxprenolol, both of which have been prescribed in large quantities over a number of years.

How does beta-blockade lower blood pressure?

It has been suggested that beta-blockade may lower blood pressure (1) by reducing both the cardiac output at rest and the increases in output induced by exercise and catecholamine activity, this adjustment leading to the resetting of cardiovascular reflexes; (2) by suppressing plasma renin activity; (3) by a central action in the brain. There are serious objections to accepting any of these three alone as explaining the mode of action.

Certainly the most obvious effect of beta-blockade is a slowing of the heart rate which is accompanied by a measurable fall in cardiac output. Unless the peripheral resistance rises, blood pressure must fall, and after a period of time the baroreceptors may reset at a lower level of activity and a sustained fall in resistance may result. This would lead to the idea that hypertensive patients with high levels of cardiac output might respond better than those with low cardiac output (Ulrych *et al.*, 1968). The resting heart rate gives some indication of the level of cardiac output. Our own analysis shows that the relation between initial heart rate, the fall of heart rate with the drug, and the fall in pressure with oxprenolol, is so variable that reduction of cardiac output alone seems unlikely to account for its hypotensive action. Not only is initial heart rate a poor guide to response to treatment (Fig.) but in addition there is little relation between the fall in heart rate that occurs with the drug and the fall in blood pressure. If a fall in cardiac output is invariable with beta blockade a fall in pressure is not.

Most beta blocking drugs have been shown to depress levels of plasma renin activity (Bühler *et al.*, 1972). The exception is pindolol (Weber *et al.*,

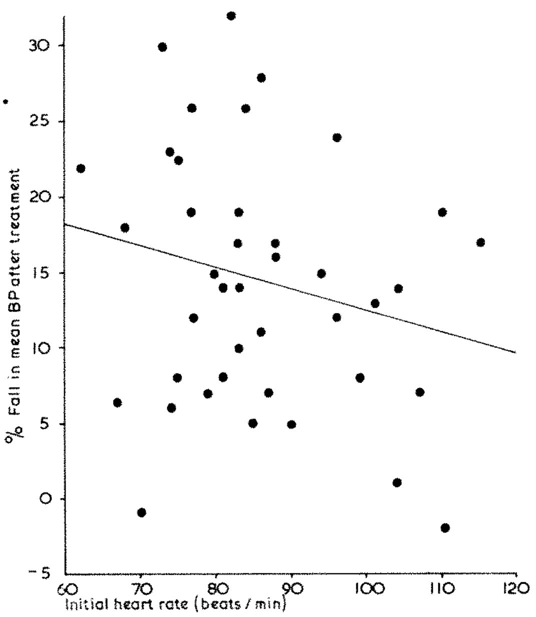

Fig. *Initial heart rate plotted against blood pressure fall in 40 patients treated with oxprenolol alone. There is a slight tendency for those with slower initial heart rates to have a greater fall in pressure (correlation coefficient −0·214, SE 0·160).*

1974). Thus the renin state of the patient could play a major part in determining the response. Indeed Bühler and co-workers, who divide their hypertensive patients into high, normal, and low renin groups, have produced evidence that the high renin group respond well to propranolol and the low renin group poorly. Other workers have failed to confirm this. Stokes *et al.* (1974) measured plasma renin activity in hypertensives treated with propranolol. They found a sustained suppression of the renin-angiotensin system during treatment, but the degree of suppression correlated poorly with the fall in blood pressure. Moreover, when pindolol was given instead of propranolol, plasma renin activity increased, but blood pressure did not. Thomas and co-workers (1976) also measured plasma renin activity and divided their hypertensive patients into three groups (according to their renin levels). All patients received oxprenolol and the falls in blood pressure were equal in each group. It seems clear, therefore, that the renin status of the patient is a poor predictor of the response to beta blockade.

A hypotensive effect mediated via the sympathetic neurones in the central nervous system has been suggested. The blood pressure in rabbits can be lowered by injecting the laevo-isomer of propranolol into the cerebral ventricle, an effect not produced by dextropropranolol which lacks beta-blocking activity (Lewis *et al.*, 1973). This possible mechanism of action needs to be further investigated in man. The fact that beta blocking drugs which freely pass the blood brain barrier are no more potent than others which do not, gives no support to this concept.

Can the physician predict good responders to beta-blockade?

There seems to be no clear answer, for age, sex, initial heart rate, and the initial height of blood pressure are not helpful in predicting the fall in blood pressure. However, if there is a satisfactory record of pretreatment blood pressure each patient's response to this form of treatment can be assessed quite quickly.

Additional agents

As the size of blood pressure fall with all the hypotensive agents is limited, it follows that the higher the initial blood pressure, the more likely it is that more than one agent will be required. If beta-blockade fails to lower blood pressure to an acceptable level, the addition of a different type of hypotensive agent can be expected to cause a further fall. The addition of a thiazide diuretic produces on average a further fall in mean blood pressure of 13 per cent with few side-effects, at the cost of one extra tablet daily (Marshall *et al.*, 1977c). The argument could be put that the rarity of symptomatic side-effects with diuretics should make them the agent of first choice. In our view preference goes to beta blocking drugs in view of their slightly greater potency, their undisputed antiarrhythmic action, and the possibility that they may reduce the incidence of myocardial infarction. A proportion of severe hypertensives will need a third or fourth agent. Success has been reported by adding methyldopa (Scott *et al.*, 1977), hydrallazine (Wilcox and Mitchell, 1977), or prazosin (Marshall *et al.*, 1977c) to treatment with beta-blocking drugs and diuretics.

There is still no escaping the element of trial and error in treating hypertension. None the less, a rational approach is easy to see. The four principles are (1) to give one agent and assess its effect; (2) the higher the initial pressure the more likely it is that more agents will be needed; (3) to choose agents in ranking order of their acceptability to the patient; (4) to aid compliance, minimise the number of tablets.

References

Barritt, D. W., and Marshall, A. J. (1977). Beta blockade in essential hypertension: an analysis of response to oxprenolol. *British Heart Journal* **39,** 825–828.

Barritt, D. W., Marshall, A. J., and Heaton, S. (1976). Comparison of oxprenolol and methyldopa in hypertension: a within-patient double-blind trial. *Lancet,* **1,** 503–505.

Bühler, F. R., Laragh, J. H., Baer, L., Vaughan, E. D., and Brunner, H. R. (1972). Propranolol inhibition of renin secretion. *New England Journal of Medicine,* **287,** 1209–1214.

Chalmers, J., Horvath, J., Tiller, D., and Bune, A. (1976). Effects of timolol and hydrochlorothiazide on blood-pressure and plasma renin activity. *Lancet* **2,** 328–331.

Davidson, C., Thadani, U., Singleton, W., and Taylor, S. H. (1976). Comparison of antihypertensive activity of beta-blocking drugs during chronic treatment. *British Medical Journal,* **2,** 7–9.

Galloway, D. B., Glover, S. C., Hendry, W. G., Logie, A. W., Petrie, J. C., Smith, M. C., Lewis, J. A., and Simpson, W. T. (1976). Propranolol in hypertension: a dose-response study. *British Medical Journal,* **2,** 140–142.

Lawrence, D. R. (1966). *Clinical Pharmacology,* 3rd ed. Churchill, London.

Lewis, P. J., Myers, M. G., Reid, J. L., and Dollery, C. T. (1973). Mechanism of beta-blockade hypotension. *New England Journal of Medicine,* **288,** 689.

Marshall, A. J., Baddeley, H., Barritt, D. W., Davies, J. D., Lee, R. E. J., Low-Beer, T. S., and Read, A. E. (1977a). Practolol peritonitis—a review of 16 cases and a survey of small bowel function in patients taking beta adrenergic blockers. *Quarterly Journal of Medicine,* **46,** 135–149.

Marshall, A. J., Barritt, D. W., and Harry, J. D. (1977b). Dose response and frequency of administration of atenolol in essential hypertension: once daily treatment with beta blockade. *Postgraduate Medical Journal* (in press).

Marshall, A. J., Barritt, D. W., Pocock, J., and Heaton, S. T. (1977c). Evaluation of beta blockade, bendrofluazide and prazosin in severe hypertension. *Lancet,* **1,** 271–274.

Marshall, A. J., Roberts, C. J. C., and Barritt, D. W. (1976). Raynaud's phenomenon as side-effect of beta-blockers in hypertension. *British Medical Journal,* **1,** 1498–1499.

Morgan, T. O., Sabto, J., Anavekar, S. N., Louis, W. J., and Doyle, A. E. (1974). A comparison of beta adrenergic blocking drugs in the treatment of hypertension. *Postgraduate Medical Journal,* **50,** 253–259.

Petrie, J. C., Galloway, D. B., Webster, J., Simpson, W. T., and Lewis, J. A. (1975). Atenolol and bendrofluazide in hypertension. *British Medical Journal,* **4,** 133–135.

Prichard, B. N. C., and Gillam, P. M. S. (1969). Treatment of hypertension with propranolol. *British Medical Journal,* **1,** 7–16.

Scott, M. E., Wilson, C., and Abdel-Mohsen, A. (1977). Atenolol and methyldopa in the treatment of hypertension. *Postgraduate Medical Journal* (in press).

Stokes, G. S., Weber, M. A., and Thornell, I. R. (1974). Beta blockers and plasma renin activity in hypertension. *British Medical Journal,* **1,** 60.

Thomas, G. W., Ledingham, J. G. G., Beilin, L. J., and Yeates, K. M. (1976). Renin unresponsiveness and the effects of oxprenolol, methyldopa and spironolactone in patients with essential hypertension. *Australian and New Zealand Journal of Medicine,* **6,** Suppl. 3, 44–48.

Ulrych, M., Frohlich, E. D., Dustan, H. P., and Page, I. H. (1968). Immediate hemodynamic effects of beta-adrenergic blockade with propranolol in normotensive and hypertensive man. *Circulation,* **37,** 411–416.

Weber, M. A., Stokes, G. S., and Gain, J. M. (1974). Comparison of the effects on renin release of beta adrenergic antagonists with differing properties. *Journal of Clinical Investigation,* **54,** 1413–1419.

Wilcox, R. G., and Mitchell, J. R. A. (1977). Studies of atenolol in association with other drugs. *Postgraduate Medical Journal* (in press).

Wilson, M., Morgan, G., and Morgan, T. (1976). The effect on blood pressure of beta adrenoceptor blocking drugs administered once daily and their duration of action when therapy is ceased. *British Journal of Clinical Pharmacology,* **3,** 857–861.

Woolfson, A. M. J., and Knapp, M. S. (1976). Once daily treatment of hypertension. *British Medical Journal,* **2,** 235.

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British Heart Journal, 1977, 39, 825-828

Beta blockade in essential hypertension: an analysis of response to oxprenolol

D. W. BARRITT AND A. J. MARSHALL

From the Bristol Royal Infirmary

The data from 40 patients with essential hypertension treated with oxprenolol alone have been used to analyse the falls of blood pressure and heart rate. Blood pressure and heart rate did not fall further as the daily dose was increased above 160 mg. The range of fall in mean pressure was from 0 to 40 mmHg and there was no clear separation into response groups. Pressure falls were unrelated to sex, age, initial heart rate, increase in heart rate on standing, the fall of heart rate with the drug, or the initial height of blood pressure. In the absence of predicting factors the use of oxprenolol, and, by deduction, other beta blocking agents, in hypertension remains empirical, but the simplification of the dose range allows the response to oxprenolol to be determined quickly.

All beta blocking drugs which have been tested in hypertension have been shown to have a hypotensive effect. In two trials propranolol, practolol, oxprenolol, metoprolol, timolol, pindolol, alprenolol, and tolamolol were found to be effective hypotensive agents (Morgan *et al.*, 1974; Davidson *et al.*, 1976), and it appears to be the case that the possession of attributes such as cardioselectivity, intrinisic sympathomimetic activity, and membrane stabilising activity are irrelevant in this respect.

Several important aspects of the use of beta blockade await clear definition. For instance, there is dispute about the dose range to be employed with the most used agents, propranolol and oxprenolol. Dose ranges for propranolol have been quoted from 10 to 4000 mg daily (Prichard and Gillam, 1969), whereas in a recent study no benefit from doubling the dose from 120 to 240 mg daily was found (Galloway *et al.*, 1976). Our initial studies with oxprenolol (Marshall and Barritt, 1973; Barritt *et al.*, 1976) adopted a dose range from 160 to 1280 mg daily, but analysis of the dose response suggested that there was no demonstrable benefit from higher dosage. The dose range must obviously be matched against the magnitude of pressure fall and exact assessment of the range of pressure fall at all levels of severity of hypertension will be an important guide to the value of the agent. In the same way the proportion of patients who will show little or no response should be ascertained. All clinicians would welcome any simple clinical analysis likely to preduct a patient's response to beta blockade.

This paper attempts to answer these questions for oxprenolol.

Patients and methods

Forty patients with essential hypertension were studied. The mean systolic blood pressure was 175 SD ± 20 and diastolic 111 SD ± 9 mmHg. The trials in which they took part have previously been reported (Marshall and Barritt, 1973; Barritt *et al.*, 1976). Seventeen were men, and 23 were women, and their age range was from 30 to 73 years. Renal disease was excluded by examining the abdomen, testing the urine for albumin, and measuring blood urea and electrolytes. Endocrine hypertension was excluded by clinical examination and measurement of urinary catecholamine excretion. The presence of obstructive airways disease, cardiac failure, or hypertensive complications requiring immediate treatment, were reasons for exclusion. All the patients were new hypertensives who had received no previous treatment, and received no other hypotensive agent during the period of study.

After the initial assessment they attended a clinic specially set aside for the study. Every patient attended this clinic on 4 occasions at weekly intervals before starting treatment. Each patient was seen throughout by the same physician and the blood pressure was measured blindly using the London School of Hygiene and Tropical Medicine sphygmomanometer. Blood pressure was measured after 5

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minutes' rest in the supine position, after standing for 2 minutes, and then after 1 minute of two-step exercise. Heart rate was also recorded. The starting dose of oxprenolol was always 80 mg twice daily. If the blood pressure did not fall to near normal levels, the dose was doubled at 2-weekly intervals, to a maximum of 1280 mg daily. The effect of treatment was assessed on three attendances at monthly intervals, when the patient was taking the maximum dose.

Statistical analysis was by correlation coefficient and Student's t test. Mean blood pressure has been calculated as follows:

$$\frac{\text{Systolic pressure} + \text{diastolic pressure} \times 2}{3}$$

In this paper, the term mean pressure always applies to this calculation.

Results

DOSE EFFECT

Neither trial whose results are further analysed in this paper was designed primarily to study dose response. In both it was assumed that if pressure fall at low dosage was inadequate, the correct step was to increase the dosage.

The final pressure fall (supine) has been related to the highest daily dose used in each of the 40 patients (160 to 1280 mg). This gives a correlation coefficient of −0·334, standard error 0·164. An individual analysis of pressure fall against dosage has been made in 14 patients who were given between 480 and 960 mg daily. The effect of increasing dosage was unpredictable. Pressure fall was plotted against the dose and the slope of the line tested for significance against zero. One patient only showed a statistically significant fall in systolic pressure, as the dose was increased, but two others showed a significant rise in diastolic pressure. Heart rates were analysed similarly. No patient showed a significant fall in heart rate with increased dosage, but one showed a significant rise. Percentage falls in mean blood pressure have been calculated for each of the 40 patients. Seven achieved falls of 25 per cent or more and each of these 7 were taking 160 mg daily.

Thus, there are no grounds for expecting that increasing the daily dose above 160 or 320 mg will lead to any further fall of pressure.

BLOOD PRESSURE FALLS RELATED TO INITIAL PRESSURES

The falls in mean blood pressure (supine) have been related to initial mean pressures. Correlation coefficient is 0·148, standard error 0·160. Thus the initial height of the blood pressure in hypertensive patients does not affect the amount of pressure fall with this drug.

PROPORTION OF GOOD AND POOR RESPONDERS

Actual falls in mean blood pressure (supine) range from −2 to 40 mmHg. Nine patients had falls from −2 to +9 mm, 11 from 10 to 19 mm, 11 from 20 to 29 mm, and 9 from 30 to 40 mm. Thus this population of 40 hypertensive patients cannot be divided into 'responders' and 'non-responders'. There is a steady progression of effectiveness in producing falls in mean blood pressure from 0 to 32 per cent. The greatest fall in average systolic pressure in any patient was from 189 to 127 mmHg and the greatest fall in diastolic pressure from 116 to 74 mmHg.

EFFECT OF OXPRENOLOL ON HEART RATES

The fall in supine heart rate was calculated at all dose levels. Fourteen patients were maintained on 160 mg daily, and 13 on 960 mg or 1280 mg daily. This allowed us to make many observations over a period of weeks at the same dose level. The mean fall in heart rate at 160 mg was 13 beats/min (SD ±8) and at 960 mg or over it was 12 (SD ±8). Similarly the mean fall in post-exercise heart rate at 160 mg daily was 24 beats/min (SD ±11), at 960 mg or over it was 21 (SD ±10). Each of these four differences was statistically significant compared with pretreatment values ($P < 0.001$). Patients in the intermediate dose range showed similar falls in heart rate. It is the case, therefore, that we failed to show any further fall in heart rate if the dose were increased above 160 mg daily.

These falls in supine and post-exercise heart rate were correlated with falls in blood pressure. The correlation coefficients were 0·089, standard error 0·160, and 0·292, standard error 0·169, respectively. We were, therefore, unable to show a relation between the fall in heart rate with oxprenolol and its hypotensive action.

PREDICTING LIKELY RESPONSE TO OXPRENOLOL

(1) Sex

In this population sex did not help to predict the fall in blood pressure.

(2) Age

Age was related to pressure fall. The correlation coefficient was 0·071, standard error 0·160. Thus pressure falls were as great in the old as the young.

(3) Initial heart rate

Supine heart rates in the pretreatment period have been correlated with the hypotensive response.

The correlation coefficient was –0·214, standard error 0·160. There was thus no tendency for those with higher initial heart rates to have a greater fall in blood pressure.

(4) Changes in heart rate with change in posture from supine to erect

Changes in heart rate on standing were correlated with the hypotensive response. The correlation coefficient was 0·300, standard error 0·160. There was thus a weak tendency for those patients whose heart rate increased on standing to have a greater fall in blood pressure with beta blockade.

(5) Does the height of pretreatment blood pressure affect size of fall with treatment?

This point has been covered in the previous section, and the result is clearly negative.

Discussion

Observations of blood pressure level and heart rates are easily distorted by the circumstances in which they are made. Throughout these studies every effort has been made to minimise observer error and the disturbing effect of attending a hospital clinic. We emphasise that 5 pretreatment observations were made, of which the first was discarded, at least three measurements were made at the final dose level, all blood pressure measurements were taken blindly by only two observers to whom the patients became well known. The clinic routine was unhurried, but there was virtually no waiting period and all of the observations were made at the same time of day. No patient included in this study received any other hypotensive medication.

Our analysis of the dose range used in these studies leads us to conclude that nothing useful is gained by increasing the daily dose above 160 or 320 mg. In planning the study we followed the convention that if the blood pressure did not fall near to normal levels at the starting dose of 80 mg twice daily, the dose would be increased up to seven times. The negative correlation –0·334 between the size of the dose and the fall in blood pressure achieved has to be explained. We favour the following explanation. Firstly, we do not think that increasing dosage above 160 mg daily is effective in lowering pressure further. Secondly, the design of the trial resulted in higher doses for those with poorer falls in pressure. Thus, those with the least fall in pressure were given the highest doses. We do not have sufficiently detailed evidence of any possible difference in dose response between 160 and 320 mg daily to make a recommendation as to which of the two doses should routinely be regarded as maximal.

We have failed to show that increasing the daily dosage had any effect on the blood pressure. Equally there are significant falls in supine and post-exercise heart rates at 160 mg daily but no further fall even though the dose be increased six times. The technique used in these studies was to count heart rates immediately after stopping a 1-minute two-step exercise. In these patients this produced in the pretreatment period heart rates in the range 90 to 140 beats per minute. The fall in heart rate with treatment allows us to conclude that with doses of 80 mg twice daily a high degree of beta blockade exists. Our recommendation is that if doses higher than 320 mg daily are given, they should only be continued if there is well-substantiated evidence in that patient that the higher dose has reduced blood pressure consistently.

Our attempt to find clinical features that might predict the patient's response to beta blockade has produced only negative answers. Neither sex nor age appears to be relevant. It might be supposed that response to beta blockade would be especially good in those patients with high levels of sympathetic activity. For this reason we have analysed resting and post-exercise heart rates together with the increase in heart rate on assuming the erect posture. No significant correlation has emerged when each of these measurements is related to blood pressure fall. Nor does the height of pretreatment blood pressure influence how much pressure will fall.

Mean blood pressure can be expected to fall by as much as 32 per cent in some patients. The potency of oxprenolol corresponds very closely to that of methyldopa (Barritt *et al.*, 1976).

There is no satisfactory explanation as to how beta blockade lowers blood pressure. If the suppression of cardiac output were the principal mode of action we would expect that there would be a clear relation between the fall in heart rate and the fall in blood pressure. The absence of any such close relation suggests to us that this is not of crucial importance.

In these studies no measurements of plasma renin have been made. Clearly the clinician prefers to observe the blood pressure fall with 160 mg daily rather than speculate on the possible response from the level of plasma renin.

Reference has already been made to the level of sympathetic tone and its suppression with this beta blocking agent. Again the evidence is against this being of prime importance.

Conclusion

Beta blockade may be effective in any patient with essential hypertension. If oxprenolol is used there is little to be gained by increasing the daily dose above 320 mg. If the level of pretreatment blood pressure exceeds 200/115 mmHg there is little chance that, with this agent alone, pressure will fall to the normal range.

References

Barritt, D. W., Marshall, A. J., and Heaton, S. (1976). Comparison of oxprenolol and methyldopa in hypertension. A within-patient double-blind trial. *Lancet*, **1**, 503–505.

Davidson, C., Thadani, U., Singleton, W., and Taylor, S. H. (1976). Comparison of antihypertensive activity of beta blocking drugs during chronic treatment. *British Medical Journal*, **2**, 7–9.

Galloway, D. B., Glover, S. C., Hendry, W. G., Logie, A. W., Petrie, J. C., Smith, M. C., Lewis, J. A., and Simpson, W. T. (1976). Propranolol in hypertension: a dose-response study. *British Medical Journal*, **2**, 140–142.

Marshall, A. J., and Barritt, D. W. (1973). Oxprenolol in hypertension. *British Journal of Clinical Practice*, **27**, 337–340.

Morgan, T. O., Sabto, J., Anavekar, S. N., Louis, W. J., and Doyle, A. E. (1974). A comparison of beta adrenergic blocking drugs in the treatment of hypertension. *Postgraduate Medical Journal*, **50**, 253–259.

Prichard, B. N. C., and Gillam, P. M. S. (1969). Treatment of hypertension with propranolol. *British Medical Journal*, **1**, 7–16.

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Improvement of myocardial metabolism in coronary arterial disease by beta-blockade

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Twenty patients with angina pectoris associated with obstructive coronary arterial disease were investigated by stressing the heart by atrial pacing. Arterial and coronary sinus blood was sampled and the time taken to provoke angina (pacing time) measured. Nine of the patients acted as a control group and did not receive beta-blocking drugs. In this group both pacing time and myocardial lactate extraction were reproducible provided that 45 minutes rest was allowed between pacing tests: we have called this period the myocardial recovery time. The 11 remaining patients were paced before and after beta-blockade, the rate being kept constant for each patient. In contrast to the control group, beta-blockade improved myocardial metabolism as shown by increased myocardial lactate extraction ($P<0{\cdot}02$) and decreased glucose extraction ($P<0{\cdot}01$). The pacing time to angina was increased ($P<0{\cdot}01$) and the degree of ST segment depression was decreased ($P<0{\cdot}05$). There was no significant effect on systolic or diastolic blood pressure, myocardial oxygen extraction, or extraction of free fatty acids and potassium.

Failure to allow adequate time for full myocardial recovery after pacing will invalidate assessment of antianginal drugs. When this precaution is taken beta-blocking drugs are seen to improve myocardial metabolism independently of their effects on heart rate and blood pressure.

Adrenergic beta-receptor antagonists are well established in the treatment of angina pectoris (Jackson *et al.*, 1975). Their beneficial effects are related to the reduction of left ventricular work by a reduction in heart rate, arterial pressure, and velocity of myocardial contraction (Robinson, 1971). By eliminating the effect of heart rate by means of atrial pacing, Balcon (1971) concluded that the main beneficial effect of propranolol and practolol was the reduction of heart rate.

The interpretation of an atrial pacing stress test relies to a large extent on the subjective sensation of chest pain. The addition of arterial and coronary sinus sampling, and particularly estimation of lactate, provides a more objective measurement of the response of the left ventricle to stress. This study demonstrates the reproducibility of the change in lactate extraction when the atrial pacing rate is constant and the time interval between successive pacing tests is also adequate. The beneficial effects of adrenergic beta-receptor antagonists in patients with obstructive coronary arterial disease is also confirmed.

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Subjects and methods

PATIENTS

Twenty patients, 16 men and 4 women, with exercise-induced angina pectoris, were studied after informed written consent. The average age was 50 years and ranged from 31 to 70 years.

Coronary angiography had previously shown narrowings greater than 50 per cent in 1 major vessel in 3 patients, in 2 vessels in 7 patients, and in 3 vessels in 10 patients. The left ventricular ejection fraction was greater than 50 per cent in all but 2 patients. Before the study they were maximally exercised under standard conditions to determine the peak exercise heart rate (Jackson *et al.*, 1975). No patient received any medication on the day of the study. Digoxin was discontinued 2 weeks previously and oral beta-blocking drugs 1 week previously. The patients were studied in the non-fasting state.

CORONARY SINUS PACING STUDY

This was performed at a different time from coronary arteriography. After the patient had rested for 45 minutes, a Zucker bipolar electrode catheter

(Zucker *et al.*, 1965), was inserted into an antecubital vein and positioned fluoroscopically 2 cm within the coronary sinus as viewed in the anteroposterior projection. The position was repeatedly checked throughout the study by fluoroscopy and injection of contrast medium. Arterial samples were obtained from a two-way tap attached to manometer tubing and a 2 in No. 19G needle which had been inserted into the femoral artery under local anaesthesia. Femoral arterial pressure was recorded throughout the study on a Mingograph 81 recorder. Both the venous catheter and arterial needle were intermittently flushed with heparinised saline except when free fatty acids (FFA) were being measured, when saline alone was used. Before pacing, at least 2 control samples were taken simultaneously from the coronary sinus and from the femoral artery. Using a battery-powered pacemaker (Devices) the heart rate was increased at 5-second intervals by increments of 10 beats a minute and then held constant at least 10 beats a minute above the peak exercise rate or the maximum predicted heart rate (Andersen *et al.*, 1971), whichever was the greater. Pacing was discontinued when the patient experienced his usual chest discomfort or pain, not breathlessness, of a severity that would stop him in his normal daily life. Blood samples were taken at peak pacing rate and at 2, 5, and 10 minutes after pacing had stopped. Electrocardiographic recordings were made throughout the study. Slight variations in methodology will be discussed with the results of each group.

MEASUREMENTS

Lactate estimations were by Livesley's modification of Hohorst's method (Livesley and Atkinson, 1974). FFA (Duncombe, 1963), oxygen saturation, potassium, and glucose, were also measured before and after pacing. The amount of ST segment depression in V5 was measured before and after pacing, disregarding the first two post-pacing beats (Parker *et al.*, 1969). A downward-sloping ST depression of at least 1 mm persisting for 0·08 s or longer was considered indicative of ischaemia (Jackson *et al.*, 1975). Myocardial extraction ratio is calculated as the difference between arterial and coronary sinus lactates divided by arterial lactate and is then expressed as a percentage. A myocardial lactate extraction of less than 10 per cent on peak pacing, or coronary sinus lactate greater than arterial lactate, indicates ischaemia (Herman *et al.*, 1967). Myocardial extractions of glucose, FFA, potassium, and oxygen were calculated in the same way. Statistical analysis employed Student's paired t test.

Results

No ill effects resulted from the investigations.

CONTROL PATIENTS

In order to assess the effects of beta-blockade, it was essential to determine the time to pain, and myocardial lactate extraction, during an initial pacing stress test and the interval between tests for a similar result to be obtained. Nine patients were paced at an identical rate for a second time at varying intervals after their initial pacing test. Only when the pacing test was repeated at an interval of at least 45 minutes after the original pacing test, were the pacing time, degree of depression of the ST segment, arteriovenous lactate difference, and myocardial lactate extraction reproducible, and the differences between the two pacing tests not statistically significant (Fig. 1, Table 1). We have called this period the myocardial recovery time (MRT). It is interesting to note that in 2 patients paced again less than 45 minutes after the initial pacing an improved result was associated with a well-developed collateral supply shown angiographically.

PATIENTS RECEIVING BETA-BLOCKERS

Six patients were restudied after intravenous tolamolol (0·15 mg/kg) and 5 after intravenous propranolol (0·1 mg/kg). Preliminary work had shown that, within 15 minutes of these drugs being given intravenously, plasma levels of the beta-blocker within the coronary sinus were stable. The drugs were injected 30 minutes after the original

Table 1 *Control pacing study: second pacing 45 minutes after the first (5 patients)*

		First pacing test	*Second pacing test*	*P*
Pacing time (s)		134 ±19·2	145 ±20·3	NS
ST depression (mm)		1·00 ±0·35	1·00 ±0·35	NS
Arteriovenous lactate difference (mg/100 ml)	Resting	2·32 ±0·43	1·92 ±0·19	NS
	Resting minus peak pacing	1·56 ±0·47	1·60 ±0·45	NS
Myocardial lactate extraction (%)		9·14 ±5·78	5·88 ±7·48	NS

All results are expressed as mean ± SE of mean.
NS = not significant.

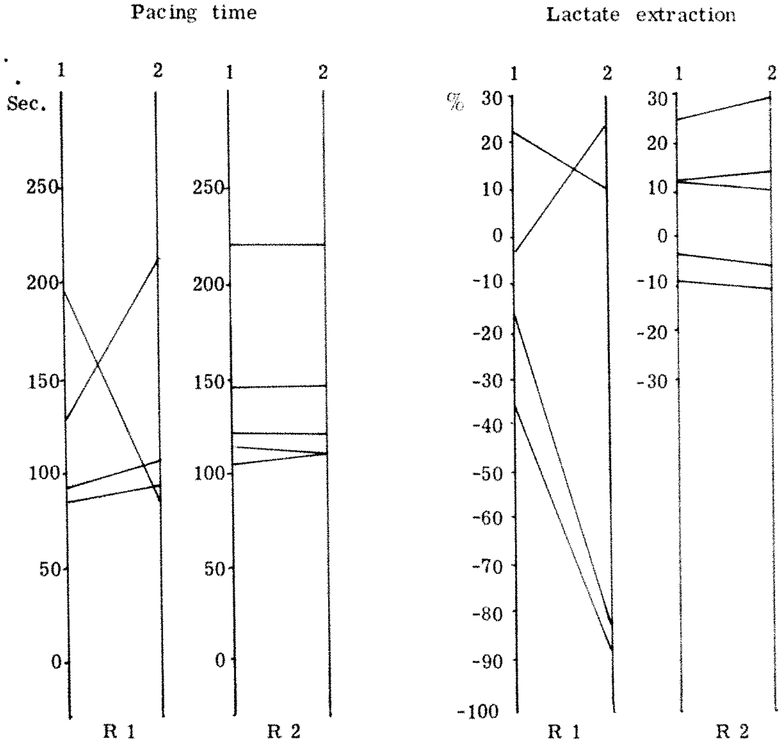

Fig. 1 *Effect of atrial pacing on pacing time and on lactate extraction. R1, interval between atrial pacing tests 1 and 2 less than 45 minutes; R2, interval greater than 45 minutes. Measurements of pacing time and lactate extraction are reproducible when the second pacing test follows 45 minutes after the initial pacing test.*

control pacing test, and 15 minutes later the atrial pacing study was repeated (Fig. 2, Table 2). In comparison with the initial control pacing test, intravenous beta-blockade significantly prolonged pacing time to pain (P<0·01), decreased postpacing ST depression (P<0·05) and glucose extraction (P<0·01), and improved myocardial lactate extraction (P<0·02). The prepacing heart rate was significantly lowered. Five patients were converted from lactate production to lactate extraction. Though beta-blockade decreased potassium extraction and increased FFA extraction, these changes were not significant at the 5 per cent level, neither was there any significant difference in myocardial oxygen extraction or prepacing systolic and diastolic arterial pressure between the control patients and those who were treated with a beta-blocker. There were no differences in lactate extraction between control and treated patients 2, 5, and 10 minutes after pacing.

Table 2 *Effect of beta-blockade on haemodynamics and myocardial metabolism (11 patients)*

		Control	*Beta-blockade*	*P*
Pacing test				
Pacing time (s)		212·0 ±30·5	288·2 ±45·9	<0·01
ST segment depression (mm)		1·65 ± 0·41	1·05 ± 0·41	<0·05
Myocardial glucose extraction (%)		12·2 ± 2·7	2·9 ± 2·6	<0·01
Myocardial lactate extraction (%)		−24·6 ±19·3	1·57 ±12·3	<0·02
Arteriovenous lactate difference (mg/100 ml)	Resting	1·64 ± 0·26	1·21 ± 0·22	NS
	Resting minus peak pacing	3·13 ± 0·87	1·24 ± 0·57	<0·002
Potassium extraction (%)		6·4 ± 1·2	2·6 ± 2·1	NS
Myocardial FFA extraction (%)*		−2·73 ±19·4	10·8 ±12·6	NS
Myocardial O_2 extraction (%)		49·9 ± 4·25	53·9 ± 5·0	NS
Prepacing				
Arterial systolic pressure (mmHg)		132·4 ± 4·3	133·3 ± 2·9	NS
Arterial diastolic pressure (mmHg)		74·6 ± 3·3	76·3 ± 1·2	NS
Resting heart rate (beats/min)		88·2 ± 3·4	77·6 ± 2·7	<0·05

All results are expressed as mean ±SE of mean.
*4 patients only.

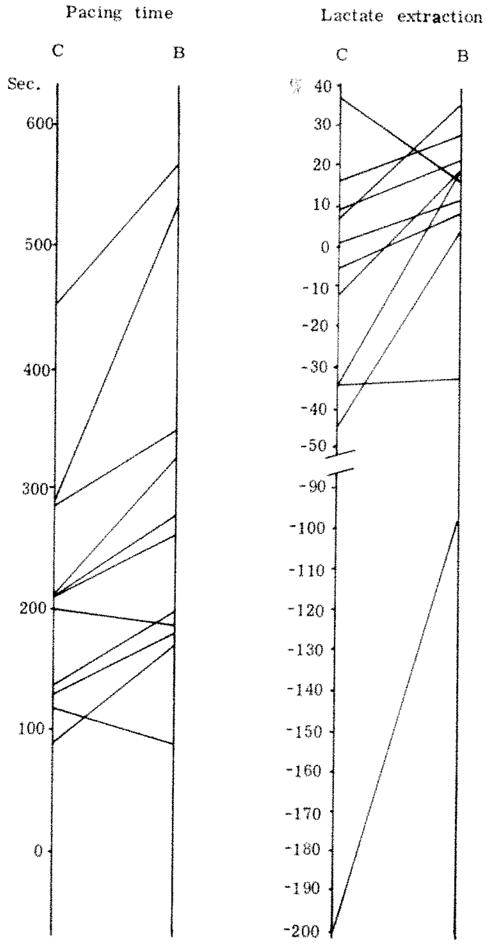

Fig. 2 *Atrial pacing stress before and after beta-blockade. Improvement in pacing time and lactate extraction by beta-blockade (B) when compared with control (C).*

Discussion

Myocardial metabolism is normally aerobic, but in the presence of ischaemia anaerobic metabolism develops. This results in a decrease in lactate extraction by the myocardium, with a resultant increase in the lactate content of the coronary sinus. Measurement of myocardial lactate extraction before and after an atrial pacing stress is a reliable means of assessing myocardial ischaemia (Gorlin, 1969). Assessment of the effect of any intervention, for example by drugs or operation, on myocardial lactate metabolism requires that on repeated control tests atrial pacing be associated with a similar time to pain and a similar change in lactate metabolism. Since atrial pacing is terminated by the subjective symptom of chest pain and the time at which this occurs will differ between patients, the degree of change in coronary AV lactate differences during atrial pacing is unique for each individual's pain: he, therefore, must act as his own control. We have shown that if a recovery time of 45 minutes is allowed, the results of an atrial pacing stress test are reproducible both in time to pain and degree of lactate extraction. Atrial pacing tests repeated before full myocardial recovery will provide misleading information on the therapeutic effectiveness of any particular agent.

After myocardial infarction, beta-blocking drugs have been shown to improve myocardial metabolism at rest (Mueller *et al.*, 1974). However, in patients with angina it was thought that an atrial pacing stress test, in which the effect of the drug on heart rate is eliminated, might fail to show any beneficial effect of beta-blocker (Balcon, 1971). In the clinical situation, improvement can be correlated with a reduction in the peak exercise heart rate (Jackson *et al.*, 1975), but we wondered whether a beneficial effect on myocardial metabolism, similar to that resulting from glyceryl trinitrate (Chiong *et al.*, 1972), was also present. We have shown that when the heart is paced at the same rate in individual patients before and after administration of beta-blocker, pacing time to angina is increased and myocardial lactate extraction significantly improved by the drug. This improvement occurred with both a cardioselective (tolamolol) and a non-selective (propranolol) beta-blocker. Decreased myocardial lactate extraction on atrial pacing may be influenced by both glucose extraction (Most *et al.*, 1972) and a change in the arterial level of FFA (Kaijser *et al.*, 1972). In this investigation beta-blockade significantly decreased glucose extraction. Myocardial ischaemia in man is associated with augmented glucose extraction (Most *et al.*, 1972), and the decrease observed here may be a further reflection of an improvement in myocardial metabolism. There was no significant change in FFA uptake, which in turn increases the sensitivity of lactate as an expression of myocardial ischaemia (Opie *et al.*, 1973).

While the beta-blockers may be improving myocardial metabolism by a direct effect at cellular level, it is also possible that they are reducing myocardial oxygen consumption at peak pacing by reducing ventricular contractility or by affecting coronary blood flow. In this study the reduction in heart rate by beta-blockers was abolished by atrial pacing and there were no changes in arterial pressure. Coronary flow in patients with and without coronary arterial disease is reduced after propranolol both at rest and after exercise. Coronary vascular resistance is increased and, associated with this, myocardial oxygen consumption is decreased (Wolfson and Gorlin, 1969); as the vasoconstrictor effect of beta-blockers is accompanied by a reduction in oxygen consumption there may be a change in distribution of myocardial blood flow from non-ischaemic to ischaemic areas (Pitt and Craven, 1970).

Beta-blockade has been shown to reduce mortality in patients after myocardial infarction (Multicentre International Study, 1975) and this may reflect an antiarrhythmic action rather than an effect on reducing the size of the infarct (Julian, 1975). We have shown that beta-blockers produce a significant improvement in myocardial metabolism during angina produced by atrial pacing, and we suggest that this action is related to the documented beneficial effects of beta-blockade on mortality.

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References

Andersen, K., Shephard, R. J., Denolin, H., Varnauskas, E., and Masironi, R. (1971). *Fundamentals of Exercise Testing*. World Health Organization, Geneva.

Balcon, R. (1971). Assessment of drugs in angina pectoris: 3. *Postgraduate Medical Journal*, **47**, Suppl. Advances in adrenergic beta-receptor therapy. 53–58.

Chiong, M. A., West, R. O., and Parker, J. O. (1972). Influence of nitroglycerin on myocardial metabolism and hemodynamics during angina induced by atrial pacing. *Circulation*, **45**, 1044–1056.

Duncombe, W. G. (1963). The colorimetric micro-determination of long-chain fatty acids. *Biochemical Journal*, **88**, 7–10.

Gorlin, R. (1969). Evaluation of myocardial metabolism in ischemic heart disease. *Circulation*, **39–40**, Suppl. IV, 155–163.

Herman, M. V., Elliott, W. C., and Gorlin, R. (1967). An electrocardiographic, anatomic, and metabolic study of zonal myocardial ischemia in coronary heart disease. *Circulation*, **35**, 834–846.

Jackson, G., Atkinson, L., and Oram, S. (1975). Reassessment of failed beta-blocker treatment in angina pectoris by peak exercise heart rate measurements. *British Medical Journal*, **3**, 616–618.

Julian, D. G. (1975). Towards preventing coronary death from ventricular fibrillation. International Lecture American Heart Association 48th Scientific Sessions (abstract). *Circulation* **51–52.** Suppl. II—1.

Kaijser, L., Carlson, L. A., Eklund, B., Nye, E. R., Rossner, S., and Wahlqvist, M. L. (1972). Substrate uptake by the ischaemic human heart during angina induced by atrial pacing. In *Effect of Acute Ischaemia on Myocardial Function. Proceedings of the 7th Pfizer International Symposium, Edinburgh*, p. 223. Ed. by M. F. Oliver, D. G. Julian, and K. W. Donald. Churchill Livingstone, Edinburgh and London.

Livesley, B., and Atkinson, L. (1974). Accurate quantitative estimation of lactate in whole blood. *Clinical Chemistry*. **20,** 1478.

Most, A. S., Gorlin, R., and Soeldner, J. S. (1972). Glucose extraction by the human myocardium during pacing stress. *Circulation*, **45,** 92–96.

Mueller, H. S., Ayres, S. M., Religa, A., and Evans, R. G. (1974). Propranolol in the treatment of acute myocardial infarction: effect on myocardial oxygenation and hemodynamics. *Circulation*, **49,** 1078–1087.

Multicentre International Study (1975). Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. *British Medical Journal*, **3,** 735–740.

Opie, L. H., Owen, P., Thomas, M., and Samson, R. (1973). Coronary sinus lactate measurements in assessment of myocardial ischemia. *American Journal of Cardiology*, **32,** 295–305.

Parker, J. O., Chiong, M. A., West, R. O., and Case, R. B. (1969). Sequential alterations in myocardial lactate metabolism, S-T segments and left ventricular function during angina induced by atrial pacing. *Circulation*, **40,** 113–131.

Pitt, B., and Craven, P. (1970). Effect of propranolol on regional myocardial blood flow in acute ischaemia. *Cardiovascular Research*, **4,** 176–179.

Robinson, B. F. (1971). The mode of action of beta-antagonists in angina pectoris. *Postgraduate Medical Journal*, **47,** Suppl. Advances in adrenergic beta-receptor therapy. 41–44.

Wolfson, S., and Gorlin, R. (1969). Cardiovascular pharmacology of propranolol in man. *Circulation*, **40,** 501–511.

Zucker, I. R., Rothfeld, E. L., and Bernstein, A. (1965). A new multipurpose cardiac catheter. *American Journal of Cardiology*, **15,** 45–47.

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Metoprolol—a new cardioselective β-adrenoceptor blocking agent for treatment of tachyarrhythmias

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The antiarrhythmic effect of the cardioselective β-adrenoceptor blocking agent metoprolol, given intravenously, was studied in 44 patients with various tachyarrhythmias, including patients with congestive heart failure and signs of digitalis intoxication. All patients with atrial tachycardia (12 cases) reverted to normal sinus rhythm. In 3 out of 18 patients with atrial fibrillation, sinus rhythm was restored, and in the others there was a significant reduction in ventricular rate. In 6 of 10 patients with ventricular ectopic beats, and 1 of 2 patients with ventricular tachycardia, the ectopic rhythm was abolished. The drug was well tolerated, without any significant changes in blood pressure, even by patients with signs of digitalis intoxication and varying degrees of pulmonary or peripheral circulatory congestion. Metoprolol is of clinical value for treatment of tachyarrhythmias, especially those of supraventricular origin.

Metoprolol is a potent cardioselective β-adrenoceptor blocking agent lacking intrinsic sympathomimetic activity and significant effects on the peripheral vascular bed (Åblad *et al.*, 1973; Johnson, 1975). We have previously studied the haemodynamic effects of metoprolol at rest and during exercise in normal subjects (Stenberg *et al.*, 1975). In the present study, we have investigated the effect of metoprolol on tachyarrhythmias of varying aetiology in patients with and without cardiac failure.

Subjects and methods

Forty-four consecutive patients, 30 men and 14 women, with various tachyarrhythmias were studied. Thirty-five had supraventricular and 9 had ventricular arrhythmias. The majority of the patients were between 20 and 40 years of age. Twenty-five patients suffered from rheumatic heart disease, 9 from ischaemic heart disease, and the remaining 10 had pericardial disease (2 cases), myocarditis (1 case), thyrotoxicosis (1 case) or idiopathic arrhythmias (6 cases). Twelve of the patients with supraventricular arrhythmias had atrial tachycardia, 5 had atrial flutter, and 18 had atrial fibrillation, in 3 combined with premature ventricular contractions. The patients with isolated ventricular arrhythmias included 7 with ventricular premature contractions and 2 with ventricular tachycardia.

Patients with systolic blood pressure less than 80 mmHg, or with gross congestive heart failure, were excluded from the study, while those with mild congestive failure, bronchospasm, or signs of digitalis intoxication were included. Of 44 patients, 30 were receiving digitalis, and 9 of these had clinical and electrocardiographic evidence of digitalis intoxication. One patient had chronic obstructive lung disease, and 2 suffered from acute myocardial infarction.

It was difficult to assess the precise duration of arrhythmia in the patients with atrial fibrillation, atrial flutter, and ventricular premature beats, but from the history this was usually several months. The duration of atrial tachycardia was less than 4 hours in 4 patients, from 4 to 8 hours in 6 patients, and more than 8 hours in the other 2. Two patients with atrial tachycardia received the drug on two occasions with an interval of several days.

After an electrocardiographic diagnosis of the arrhythmia had been made, the electrocardiograms of the patients were continuously monitored. The study was said to have started when persistent arrhythmia had been observed over a period of at least 1 hour, during which time other antiarrhythmic drugs had been tried in several patients. Metoprolol was given intravenously in a dose of 0·15 mg per kg body weight at a rate of 1 mg per minute. The

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Table 1 *Effect of intravenous metoprolol in atrial fibrillation and flutter*

Case No.	*Age and sex*	*Weight (kg)*	*Diagnosis*	*Dose of metoprolol (mg)*	*Heart rhythm*		*Ventr. rate*		*Blood pressure (mmHg)*		*Onset of action (min)*	*Remarks*
					Before	*After*	*Before*	*After*	*Before*	*After*		
1	59 M	59	RHD, MS	8	AF	AF	160	90	120/80	120/80	2	NSR 7 days afterwards on oral metoprolol
2	20 M	40	RHD, MS, MR	6	AF	AF	150	115	115/80	120/80	10	—
3	55 M	55	RHD, MS, MR	8	AF	AF	140	85	110/70	115/70	10	—
4	60 F	50	RHD, MS, AS, AR, CHF	5	AF	AF	110	60	150/80	160/80	10	NSR after 12 h; unchanged CHF
5	29 F	64	RHD, MS, MR	9·5	AF	AF	126	98	120/80	110/80	10	—
6	16 F	33	RHD, MS, TR, dig. intox.	5	AF PVC	AF	110	84	110/80	90/70	2	PVC disappeared after metoprolol
7	36 F	35	RHD, MS, MR, dig. intox.	5·5	AF	AF	102	66	120/80	110/70	5	—
8	33 M	56	RHD, MS, MR	7·5	AF	AF	114	85	105/75	105/70	10	—
9	28 F	65	RHD, MS	9	AF PVC	AF	162	114	105/70	100/70	10	PVC (6–8/min) disappeared at 40 min
10	25 M	60	RHD, MS, dig. intox.	9	AF PVC	AF	165	120	130/70	110/80	5	No change in PVC (5–8/min)
11	24 M	45	RHD, MR	6·5	AF	AF	160	140	120/70	110/60	15	—
12	38 F	42	RHD, MS	6	AF	NSR	160	100	120/80	125/80	5	NSR after 5 min
13	45 F	30	RHD, MS	4·5	AF	AF	150	90	110/75	100/65	5	—
14	27 M	50	RHD, MS	7·5	AF	AF	140	110	120/80	120/75	2	—
15	22 M	47	RHD, MS, MR	7	AF	AF	147	48	150/30	130/30	15	—
16	20 M	40	RHD, MS, MR	6	AF	AF	114	87	115/80	105/80	5	—
17	20 M	55	Constrictive pericarditis	8·25	AF	AF	108	60	115/80	110/80	10	—
18	36 M	40	RHD, MS, TR, dig. intox.	6	AFL	AFL	120	78	120/75	110/70	5	No change in atrial rate (280/min)
19	35 M	50	RHD, MS	7·5	AFL	AFL	150	150	100/80	100/80	—	No response; atrial rate unchanged (300/min)
20	60 M	45	Pericardial effusion	6·75	AFL	AFL	130	120	120/70	110/70	5	No change in atrial rate (350/min); after 14 h→NSR
21	41 M	46	RHD, MS	7	AFL	AFL	90	70	110/80	105/80	5	No change in atrial rate (330/min); occasional PVC after metoprolol
22	34 M	50	Thyrotoxicosis	7·5	AF	NSR	200	75	120/80	125/80	5	After 9 h→NSR
23	40 M	70	RHD, MS, MR, TR, CHF	10	AFL	AFL	140	100	100/70	100/70	5	No change in atrial rate (280/min)

Abbreviations: Diagnosis: AR, aortic regurgitation; AS, aortic stenosis; CHF, chronic heart failure; MR, mitral regurgitation; MS, mitral stenosis; RHD, rheumatic heart disease; TR, tricuspid regurgitation. *Heart rhythm:* AF, atrial fibrillation; AFL, atrial flutter; NSR, normal sinus rhythm; PVC, premature ventricular contractions.

cardiac rhythm, heart rate, blood pressure, and clinical condition were continuously monitored. Electrocardiograms were obtained at 10-minute intervals for 1 hour after the injection, and then at hourly intervals for the next 12 hours.

Results

Pertinent clinical data and the results of treatment with metoprolol are given in Tables 1 to 3 and Fig. 1 and 2. In 17 patients the cardiac rhythm was restored to normal, while in 23 patients there was a beneficial response, i.e. either the heart rate dropped to normal or the ectopic activity was much reduced (Fig. 1). In four patients there was no response. Twenty patients responded in less than 10 minutes, 14 patients in 10 to 19 minutes, and 6 patients in over 20 minutes (Fig. 2).

ATRIAL TACHYARRHYTHMIAS

All patients with paroxysmal atrial tachycardia whatever the aetiology and duration reverted to normal sinus rhythm (Table 2); two of these patients received the drug a second time several days later with the same result. On 8 occasions

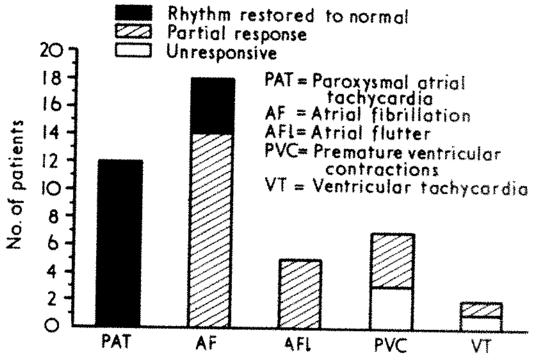

Fig. 1 *Results of treatment with intravenous metoprolol in patients with various cardiac arrhythmias.*

Table 2 *Effect of intravenous metoprolol in paroxysmal atrial tachycardia*

Case No.	*Age and sex*	*Weight (kg)*	*Diagnosis*	*Dose of metoprolol (mg)*	*Heart rhythm*		*Ventr. rate*		*Blood pressure (mmHg)*		*Onset of action (min)*	*Remarks*
					Before	*After*	*Before*	*After*	*Before*	*After*		
1	35 M	60	Idiopathic	9	PAT	NSR	166	80	100/80	90/70	30	—
2	20 M	45	RHD, MI, AI	6·75	PAT	NSR	200	100	140/20	120/20	10	Unresponsive to mechanical stimulation of vagus, digitalis, and practolol; 2nd trial diff. day
3	22 F	60	Idiopathic	9	PAT	NSR	160	108	110/70	100/70	5	—
4	25 M	37	RHD, op. MS	5·5	PAT	NSR	190	93	95/60	85/60	20	—
5	34 M	64	Idiopathic	9	PAT	NSR	220	120	120/75	110/75	5	Unresponsive to mechanical stimulation of vagus and digitalis
6	15 F	35	RHD, MS, MI	6	PAT	NSR	190	100	100/80	110/70	10	Decrease in atrial rate to 160/min at 5 min; NSR at 10 min
7	18 F	40	Myocarditis, CHF dig. intox.	6	PAT	NSR	180	80	100/60	90/60	20	Gross CHF and cardiomegaly
8	36 F	40	Op. MS; dig. intox.	6	PAT	NSR	180	72	100/70	110/75	10	Success also at second trial later
9	51 F	60	Intracranial tumour	9	PAT	NSR	190	130	130/80	120/80	5	Persistent sinus tachycardia after PAT abolished
10	14 M	50	WPW syndrome	8	PAT	NSR	210	75	120/80	120/80	30	At 30 min sinus bradycardia (30–60/min) alternating with PAT; at 45 min stabilisation at NSR 76–80 min
11	34 M	60	Idiopathic	9	PAT	NSR	180	100	120/90	120/80	10	PAT developed while on oral practolol (100 mg b.d.)
12	38 M	46	MS, dig. intox.	7	PAT	NSR	180	90	100/70	100/70	20	—

Abbreviations: See Table 1. PAT, paroxysmal atrial tachycardia.

Table 3 *Effect of intravenous metoprolol in ventricular tachyarrhythmias*

Case No.	*Age and sex*	*Weight (kg)*	*Diagnosis*	*Dose of metoprolol (mg)*	*Heart rhythm*		*Ventr. rate*		*Blood pressure (mmHg)*		*Onset of action (min)*	*Remarks*
					Before	*After*	*Before*	*After*	*Before*	*After*		
1	46 M	60	AMI	9	VT	NSR	180	100	80/50	80/50	5	No response to lignocaine procainamide, ajmaline, and practolol; VT for several h
2	50 M	60	CHD	8	SR PVC	NSR	72	60	110/70	100/70	2	PVC initially 30/min; disappeared at 5 min, but reappeared after 45 min
3	60 F	60	CHD, AMI	9	SR PVC	NSR	120	84	130/90	120/80	2	PVC initially 40/min; disappeared completely
4	33 M	52	Idiopathic	8	SR PVC	SR PVC	100	96	130/90	120/90	—	No effect; no response to ajmaline, practolol, lignocaine, atropine, propranolol, and phenytoin
5	62 M	70	CHD, emphysema, and chronic bronchitis	10	SR PVC	NSR	110	78	160/70	150/70	5	Junctional and PVC initially 30/min, disappeared completely
6	55 F	60	CHD, diabetes	9	VT	VT	165	165	80/?	80/?	—	No response
7	40 M	70	CHD	10	SR PVC	SR PVC	123	81	130/80	135/80	20	Partial response, PVC reduced from 30 to 6/min
8	64 M	65	CHD	10	SR PVC	SR PVC	114	75	160/50	150/50	—	No change in PVC 24/min; earlier also procainamide, lignocaine, and phenytoin without response
9	49 M	80	CHD	10	SR PVC	SR PVC	80	70	100/60	100/70	—	No change in PVC 20/min

Abbreviations: See Table 1. AMI, acute myocardial infarction; CHD, coronary heart disease; VT, ventricular tachycardia; SR, sinus rhythm.

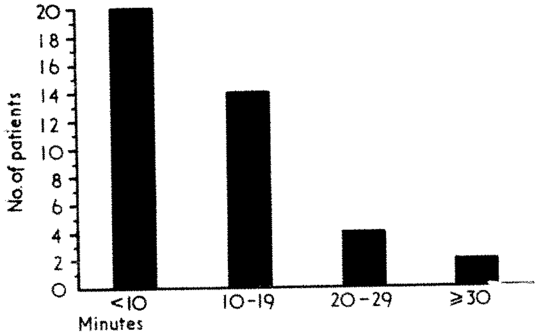

Fig. 2 *Time until response after intravenous metoprolol in patients with various cardiac arrhythmias.*

reversion to normal rhythm occurred within 10 minutes, on 4 occasions within 20 minutes, and in 2 patients 30 minutes after injection of the drug.

Of the 18 patients with atrial fibrillation, 2 reverted to sinus rhythm within 5 minutes after the injection, and 1 was in normal rhythm 12 hours afterwards (Table 1). In the remaining 15 patients the atrial fibrillation persisted, though the ventricular rate decreased from an average of 140 per minute (102 to 200 per minute) before therapy to an average of 90 per minute (48 to 140 per minute). In 2 out of 3 patients with associated ventricular ectopic beats these disappeared after metoprolol. The degree of atrioventricular block increased in 4 of 5 patients with atrial flutter, thus decreasing the ventricular rate.

VENTRICULAR TACHYARRHYTHMIAS

Of 10 patients with ventricular ectopic beats, 6 became completely free from their arrhythmia after the administration of metoprolol (Table 3), including 2 who were in atrial fibrillation (Table 1). In 1 further patient the number of ectopic beats decreased significantly from 30 to 6 per minute.

One of the two patients with ventricular tachycardia reverted to normal sinus rhythm less than 5 minutes after the injection. This patient (case 1) was suffering from an acute myocardial infarction with shock, and his arrhythmia had previously failed to respond to lignocaine, procainamide, ajmaline, and practolol; no further fall of blood pressure was observed.

SIDE EFFECTS

No side effects were observed in any patient, and there were no significant changes in blood pressure. In patients with congestive heart failure, the pulmonary congestion did not increase, and there was no deterioration in pulmonary function in the patient with chronic obstructive lung disease and junctional and ventricular ectopic beats.

Discussion

β-adrenoceptor blocking agents have become established drugs for the treatment of cardiac arrhythmias, and their use for this purpose has been extensively reviewed by Singh and Jewitt (1974) and Wit *et al.* (1975a, b, c). Of the various β-adrenoceptor blocking agents available propranolol has been most commonly used, and is of proven value in, for example, arrhythmias complicating acute myocardial infarction (Lemberg *et al.*, 1970). However, the drug has a significant negative inotropic action on the heart and may also cause bronchial constriction (Stephen, 1966), and this will limit the use of propranolol in patients with manifest or threatening bronchospasm or cardiac failure. Such risks are considerably less with practolol, which also has a proven value as an antiarrhythmic agent (Gibson *et al.*, 1968; Jewitt *et al.*, 1969; Gent *et al.*, 1970). Unfortunately, however, practolol has the well-known drawback of causing severe immune reactions when used over prolonged periods (*British Medical Journal*, 1975), and this has substantially limited its clinical usefulness.

Metoprolol, another cardioselective β-adrenoceptor blocking agent, has in earlier studies in animals and man been found to be a potent drug largely devoid of any influence on the smooth muscles of the bronchioles (Åblad *et al.*, 1975). Hence, this drug was used in the present study even in patients with pulmonary congestion, low arterial blood pressure, and airways obstruction. Metoprolol was found to be effective in all cases of paroxysmal atrial tachycardia, and produced significant decreases in heart rate in cases of atrial fibrillation and flutter. Cardiac rhythm was restored to normal in 3 out of 18 patients with atrial fibrillation. The number of patients with ventricular arrhythmias was small, but it is of interest to note that in 6 out of 10 cases the ventricular premature beats disappeared, and in one further patient a significant reduction in the frequency of ectopic beats was observed. Moreover, 1 of the 2 patients with ventricular tachycardia associated with shock secondary to acute myocardial infarction reverted to normal rhythm after previous failure to respond to administration of lignocaine, ajmaline, procainamide, and practolol.

Clinical experience with metoprolol in patients with cardiac arrhythmias has not previously been reported. In a similar study using practolol 5 out of 6 episodes of paroxysmal atrial tachycardia, and 4 out of 7 instances of ventricular ectopic beats responded to practolol (Manjuran *et al.,* 1977). Thus, the results with practolol appear to be similar to those in the present study, but the number of patients in the former study was only 27.

Clinically, the use of metoprolol has so far been reported only in hypertensive patients (Bengtsson, 1976; Sannerstedt and Wasir, 1977). In the present study, however, metoprolol was found to be a useful antiarrhythmic agent and virtually free from side effects. It may safely be given even to patients with congestive heart failure, signs of digitalis intoxication, and bronchial obstruction.

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References

Åblad, B., Borg, K. O., Carlsson, E., Ek, L., Johnson, G., Malmfors, T., and Regårdh, C.-G. (1975). A survey of the pharmacological properties of metoprolol in animals and and man. *Acta Pharmacologica et Toxicologica,* **36,** Suppl. V, 7–23.

Åblad, B., Carlsson, E., and Ek, L. (1973). Pharmacological studies of two new cardioselective adrenergic beta-receptor antagonists. *Life Sciences,* **12,** 107–119.

Bengtsson, C. (1976). Comparison between metoprolol and propranolol as antihypertensive agents. A double-blind crossover study. *Acta Medica Scandinavica,* **199,** 71–74.

British Medical Journal (1975). Editorial. Side effects of practolol. **2,** 577–578.

Gent, G., Davis, T. C., and McDonald, A. (1970). Practolol in treatment of supraventricular cardiac dysrhythmias. *British Medical Journal,* **1,** 533–535.

Gibson, D. G., Balcon, R., and Sowton, E. (1968). Clinical use of I.C.I. 50172 as an antidysrhythmic agent in heart failure. *British Medical Journal,* **3,** 161–163.

Jewitt, D. E., Mercer, C. J., and Shillingford, J. P. (1969). Practolol in the treatment of cardiac dysrhythmias due to acute myocardial infarction. *Lancet,* **2,** 227–230.

Johnson, G. (1975). Influence of metoprolol and propranolol on hemodynamic effects induced by adrenaline and physical work. *Acta Pharmacologica et Toxicologica,* **36,** Suppl. V, 59–68.

Lemberg, L., Castellanos, A., and Arcebal, A. G. (1970). The use of propranolol in arrhythmias complicating acute myocardial infarction. *American Heart Journal,* **80,** 479–487.

Manjuran, R. J., Wasir, H. S., Bhatia, M. L., and Roy, S. B. (1977). Practolol, a cardioselective beta-adrenergic blocking agent in the treatment of diverse tachyarrhythmias. *Indian Heart Journal,* in press.

Sannerstedt, R., and Wasir, H. (1977). Acute haemodynamic effects of metoprolol in hypertensive patients. *British Journal of Clinical Pharmacology,* **4,** 23–26.

Singh, B. N., and Jewitt, D. E. (1974). β-adrenergic receptor blocking drugs in cardiac arrhythmias. *Drugs,* **7,** 426–461.

Stenberg, J., Wasir, H., Amery, A., Sannerstedt, R., and Werkö, L. (1975). Comparative hemodynamic studies in man of adrenergic β-receptor blocking agents without (H 93/26 = metoprolol) or with (H 87/07) intrinsic sympathicomimetic activity. *Acta Pharmacologica et Toxicologica,* **36,** Suppl. V, 76–84.

Stephen, S. A. (1966). Unwanted effects of propranolol. *American Journal of Cardiology,* **18,** 463–468.

Wit, A. L., Hoffman, B. F., and Rosen, M. R. (1975a). Electrophysiology and pharmacology of cardiac arrhythmias. IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade. Part A. *American Heart Journal,* **90,** 521–533.

Wit, A. L., Hoffman, B. F., and Rosen, M. R. (1975b). Electrophysiology and pharmacology of cardiac arrhythmias. IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade. Part B. *American Heart Journal,* **90,** 665–675.

Wit, A. L., Hoffman, B. F., and Rosen, M. R. (1975c). Electrophysiology and pharmacology of cardiac arrhythmias. IX. Cardiac electrophysiologic effects of beta adrenergic receptor stimulation and blockade. Part C. *American Heart Journal,* **90,** 795–803.

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Mitral valve closure index
Echocardiographic index of severity of mitral stenosis

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A new echocardiographic index of mitral valve diastolic closure, based on the rate of diastolic apposition of the anterior and posterior mitral leaflet echoes, was measured in 40 patients with mitral stenosis. This mitral valve closure index correlated highly significantly with the mitral valve orifice area (calculated from the Gorlin formula) ($r=0.87$). Correlation between the diastolic closure rate (based on the EF slope) and the calculated valve area was poor ($r=0.37$).

It is proposed that the mitral valve closure index excludes movement extraneous to the mitral apparatus and expresses the actual rate of valve closure, thus avoiding some of the factors known to contribute to the poor specificity of the diastolic closure rate. The better correlation of the mitral valve closure index with the calculated valve orifice area makes it possible to assess the severity of mitral stenosis by echocardiogram with greater accuracy and confidence.

The echocardiogram provides substantive evidence of organic mitral valve disease when its presence is only suspected or clinically undetected. It also provides surgically important information on the thickness and pliability of the valve leaflets and size of the left ventricular outflow tract. In the assessment of the functional severity of mitral stenosis the echocardiogram has so far made no definite contribution. Several investigators (Edler, 1967; Effert, 1967; Gustafason, 1967) proposed that the diastolic closure rate based on the EF slope of the anterior leaflet of the mitral valve reflects the severity of mitral stenosis but, like others (Mary *et al.*, 1973; Cope *et al.*, 1975), we found it to be insensitive and often misleading in individual patients. We report here a new index of mitral valve closure, derived from the rate at which the anterior and posterior leaflet echoes approximate, which correlates with the severity of the mitral stenosis sufficiently well to be of clinical value.

Methods

Forty patients with dominant mitral stenosis were studied by cardiac catheterisation and echocardiography. The mitral valve area was calculated using the Gorlin formula (Gorlin and Gorlin, 1951). Cardiac output was estimated by duplicate indocyanine green dye dilution curves. Direct left atrial pressure by the transeptal technique was obtained in all cases and the mean mitral gradient over 10 cycles was measured by planimetry of simultaneous left atrial and left ventricular pressure recordings. Left ventriculography excluded significant mitral regurgitation in all cases.

Echocardiograms were obtained with a Smith-Kline Ekoline 20 Ultrasonoscope and a 7·5 cm focused transducer with a frequency rate of 2·25 MHz and recorded on a Cambridge Multichannel photographic strip chart recorder. Particular care was taken to record the mitral echo where the anterior leaflet excursion was maximal and where the posterior leaflet echo was continuously present. The diastolic closure rate (DCR) of the anterior mitral leaflet was measured by the standard method (Feigenbaum, 1972). The EF slope is generally a single measurement when the anterior mitral leaflet is recorded at the level of maximum excursion (Rodger and Sumner, 1975). Where biphasic movement is seen, we have taken the earlier slope as suggested by Ross (1972). The distance between the anterior and posterior mitral leaflet echoes was measured at early (X_1), and at end diastole (X_2) in atrial fibrillation or at the point of minimal separation in mid diastole in the presence of sinus rhythm. A mitral valve closure index (MVCI) was obtained by dividing X_1–X_2 by the time (t) over which closure had occurred and expressing it as a percentage of

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the initial leaflet separation, i.e.

$$\mathrm{MVCI} = \frac{X_1 - X_2}{t \times X_1} \times 100\%$$

(Fig. 1). When the diastolic descent of both anterior and posterior mitral leaflet echoes are strictly linear, the MVCI can be simply expressed as the difference tween the two diastolic closure rates divided by the initial mitral leaflet separation i.e.

$$\mathrm{MVCI} = \frac{\mathrm{DCRa} - \mathrm{DCRp}}{X_1} \times 100\ \%$$

Results

In the 40 patients studied, the age ranged from 28 to 69 years, with 31 women and 9 men. Twelve patients were in sinus rhythm, and the remainder were in atrial fibrillation. All degrees of severity of mitral stenosis were encountered—the calculated mitral valve area ranging from 0·4 cm^2 to 3·8 cm^2. The diastolic closure rate (EF slope) correlated poorly with the calculated valve area (MVA) ($r = 0{\cdot}37$) (Fig. 2). In the same patients, the correlation between the mitral valve closure index and the calculated valve area was much better ($r = 0{\cdot}87$ (Fig. 3). The regression equation was MVCI = 33 MVA–12 ($P < 0{\cdot}001$). The patients were assigned into three groups of severe, moderate, and mild stenosis in the same way as has been done by previous investigators (Cope *et al.*, 1975), with calculated valve areas of < 1·3 cm^2, 1·3 to 1·8 cm^2, and > 1·8 cm^2, respectively (Fig. 4). The mean values of the mitral valve closure index for the three groups were 13, 49, and 74, respectively, with highly significant differences between the means: $P < 0{\cdot}001$ both between severe and moderate, and severe and mild, and $P < 0{\cdot}005$ between moderate and mild stenosis.

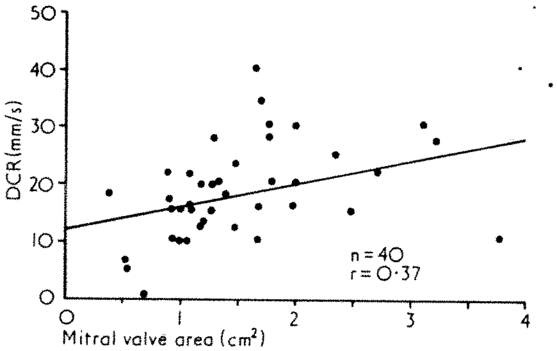

Fig. 2 *Relation between diastolic closure rate (DCR) and calculated mitral valve area in 40 patients with dominant mitral stenosis. The correlation was poor with* $r = 0{\cdot}37$.

None of the patients with a mitral valve closure index above 40 had severe stenosis. All the patients with mild stenosis had a mitral valve closure index over 50, though 6 of them could have been misdiagnosed as severe mitral stenosis with diastolic closure rates below 25 mm/s. This more sensitive

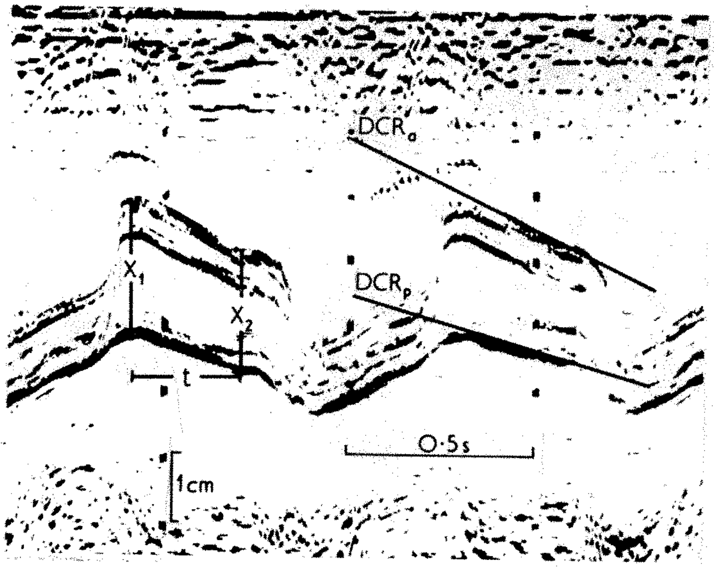

Fig. 1 *The mitral valve closure index (MVCI) is calculated as*

$$MVCI = \frac{X_1 - X_2}{t \times X_1} \times 100\ \%$$

Where X_1 *and* X_2 *represent anterior and posterior mitral leaflet separation in early* (X_1) *and end* (X_2) *diastole (or before atrial contraction in cases of sinus rhythm, as here), and t-time, in seconds, between* X_1 *and* X_2. *Alternatively*

$$MVCI = \frac{DCRa - DCRp}{X_1} \times 100\ \%$$

where DCRa and DCRp are the diastolic closure rate of the anterior and posterior leaflet echo, respectively.

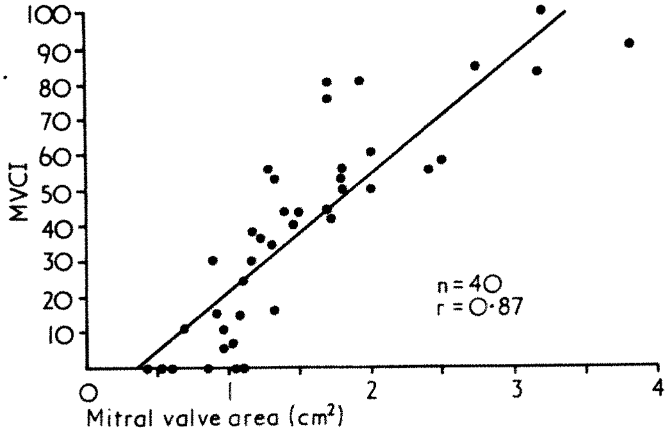

Fig. 3 *Relation between the mitral valve closure index (MVCI) and mitral valve area in the same 40 patients as in Fig. 2. The correlation is highly significant (r=0·87), the regression equation being MVCI=33 MVA–12.*

discrimination by the mitral valve closure index is also seen in Fig. 5, which shows the echocardiograms of 3 patients with severe, moderate, and mild stenosis (MVA 1·0 cm², 1·5 cm², and 2·0 cm², respectively), all of whom also had a diastolic closure rate below 20 mm/s. Their mitral valve closure index were clearly different, being 10, 43, and 80, respectively, reflecting the different rates of true valve closure.

Discussion

In the normal heart, the anterior and posterior mitral valve leaflets reach maximum separation in early diastole after which rapid closure occurs so that they are virtually apposed in mid-diastole (Rushmer *et al.*, 1956). This yields a mitral valve closure index value of the order of several hundred (Fig. 6). By contrast, in mitral stenosis, a persistent gradient of pressure across the valve results in delayed closure (Zaky *et al.*, 1968). The reduction in the rate of valve closure would be expected to reflect the severity of the mitral obstruction. In very severe stenosis, the valve would remain fully open throughout diastole, giving a mitral valve closure index of zero.

The diastolic movement of the anterior mitra leaflet echo is thought to reflect both valve movement and movement of the ring, the latter being profoundly influenced by cardiac output, heart size, and left ventricular filling (Zaky *et al.*, 1968). With increasing stenosis, diastolic closure rate reflects leaflet movement less and ring movement more (Chakorn *et al.*, 1972), a fact which certainly contributes to the poor correlation between diastolic closure rate and mitral valve area (Cope *et al.*, 1975). Zaky *et al.* (1968) suggested that a reasonable estimate of valve closure can be made by subtracting the ring excursion from the diastolic closure rate, but this presents practical difficulties because with single beam echocardiograms simultaneous recording of the two structures is not possible. On the other hand, simultaneous anterior and posterior mitral leaflet echoes can be obtained in the majority of patients with mitral stenosis, and measurement of the rate of approximation of the two echoes would be expected to give actual closure movement of the valve. The exclusion of any movement extraneous to the mitral valve apparatus by this method of measurement may well explain the better correlation of the mitral valve closure index with the calculated mitral valve area

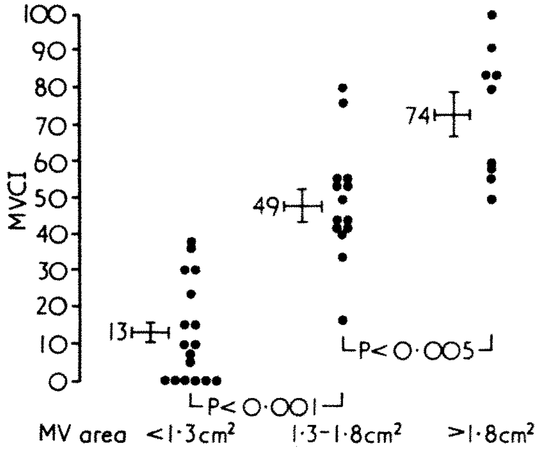

Fig. 4 *Distribution of the mitral valve closure index (MVCI) in severe, moderate, and mild mitral stenosis. Mean values are shown in figures and bars, together with the standard error. The P values of the differences between the means are shown.*

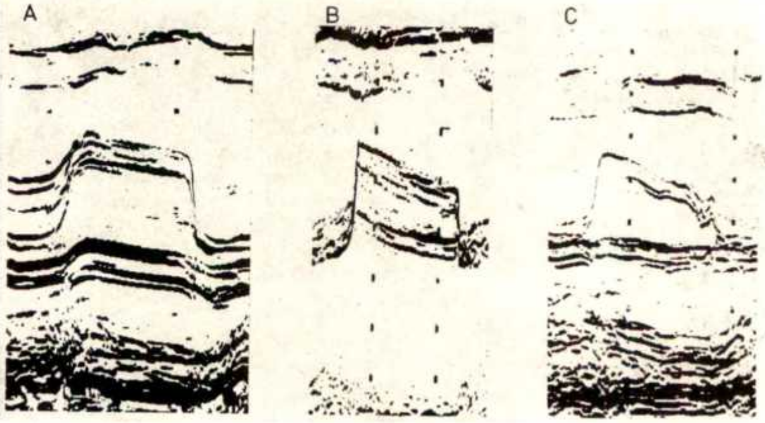

Fig. 5 *Echocardiogram from 3 patients with mitral valve areas of A, 1·0 cm², B, 1·5 cm², and C, 2·0 cm². The diastolic closure rate was below 20 in each instance, but the mitral valve closure indices were A, 10, B, 43, and C, 80, clearly denoting severe, moderate, and mild stenosis respectively.*

compared with that of the diastolic closure rate. The effect of extraneous movement on the diastolic closure rate is shown in the echocardiogram of a patient with severe stenosis (Fig. 7) in whom the diastolic closure rate varied 0 to 15 mm/s with successive beats. The mitral valve closure index was zero in every beat because the posterior leaflet echo was parallel to that of the anterior. The poor specificity of the diastolic closure rate is particularly important in patients with mild mitral stenosis. For example, a diastolic closure rate of less than 25 mm/s has been suggested as indicating moderately severe mitral stenosis (Feigenbaum, 1972), yet 6 of our patients with calculated mitral valve area ranging from 2·0 cm² to 3·8 cm² had a diastolic closure rate below that value. A correct assessment was possible with the mitral valve closure index since this was above the severe stenosis range in all six.

We have found the mitral valve closure index to be a reliable index of the mitral valve area throughout the whole range of mitral stenosis. A mitral valve closure index of 20 or less was invariably associated with severe mitral stenosis, and mitral valve closure index of over 80 excluded significant stenosis (mitral valve area >1·8 cm²).

In conclusion, previous attempts to correlate echocardiographic indices with the severity of

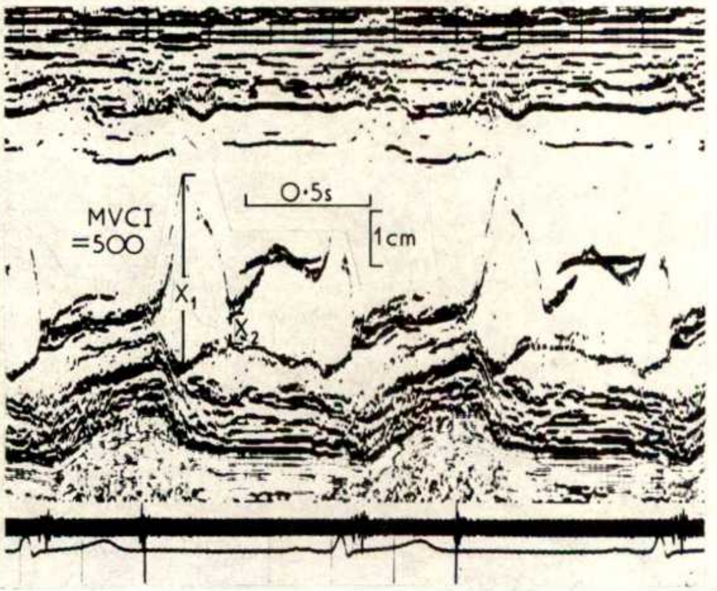

Fig. 6 *Normal mitral echogram showing rapid combined diastolic closure movement of the anterior and posterior leaflets, giving a mitral valve closure index of 500.*

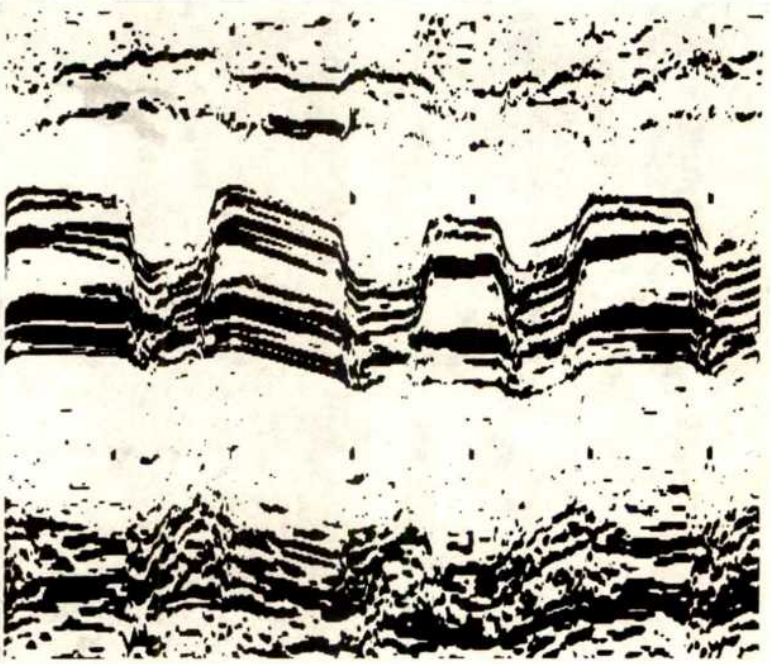

Fig. 7 *Echocardiogram from a patient with severe mitral stenosis ($MVA = 0{\cdot}6\ cm^2$). The diastolic closure rate varied from 0 to 15 mm/s between successive beats despite no true valve closure movement (i.e. $MVCI = 0$) in each beat.*

mitral stenosis have been unsuccessful and have not justified the substitution of echocardiography for the cardiac catheterisation in the preoperative assessment of patients. In the study, we have established that an index derived from the rate of apposition of the mitral leaflet echoes expresses the fundamental haemodynamic disturbance in mitral stenosis. The index correlated highly significantly with the calculated mitral valve area suggesting that this non-invasive method of quantifying mitral stenosis is accurate and reliable.

I thank Dr. M. M. Webb-Peploe and Dr. B. S. Jenkins for their encouragement and advice on the preparation of this paper.

References

Chakorn, S. A., Siggers, D. C., Wharton, C. F. P., and Deuchar, D. C. (1972). Study of normal and abnormal movements of mitral valve ring using reflected ultrasound. *British Heart Journal,* **34,** 480–486.

Cope, G. D., Kisslo, J. A., Johnson, M. L., and Behar, V. S. (1975). A reassessment of the echocardiogram in mitral stenosis. *Circulation,* **52,** 664–670.

Edler, I. (1967). Ultrasoundcardiography in mitral valve stenosis. *American Journal of Cardiology,* **19,** 18–31.

Effert, S. (1967). Pre- and post-operative evaluation of mitral stenosis by ultrasound. *American Journal of Cardiology* **19,** 59–65.

Feigenbaum, H. (1972). *Echocardiography.* Lea and Febiger, Philadelphia.

Gorlin, R., and Gorlin, S. G. (1951). Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I. *American Heart Journal,* **41,** 1–29.

Gustafson, A. (1967). Correlation between ultrasoundcardiography haemodynamics and surgical findings in mitral stenosis. *American Journal of Cardiology,* **19,** 32–41.

Mary, D. A. S., Pakrashi, B. C., Wooler, G. H., and Ionescu, M. I. (1973). Study with reflected ultrasound of patients with mitral valve repair. *British Heart Journal,* **35,** 480–487.

Rodger, J. C., and Sumner, D. J. (1975). Measurement of diastolic closure rate of normal mitral valve. *British Heart Journal,* **37,** 504–513.

Ross, F. G. M. (1972). Ultrasonic investigation of the heart. In *Ultrasonics in Clinical Diagnosis,* p. 120. Ed. by P. N. T. Wells. Churchill Livingstone, Edinburgh and London.

Rushmer, R. F., Finlayson, B. L., and Nash, A. A. (1956). Movements of the mitral valve. *Circulation Research,* **4,** 337–342.

Zaky, A., Nasser, W. K., and Feigenbaum, H. (1968). Study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis. *Circulation,* **37,** 789–799.

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Diagnosis of ventriculo-arterial discordance (transposition of the great arteries) by contrast echocardiography

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The constant anatomical relation of the aortic arch and the pulmonary artery bifurcation permits echocardiographic differentiation of the two great arteries when viewed from the suprasternal notch. When this technique was employed with contrast echocardiography in 12 infants, 6 of whom had ventriculo-arterial discordance (transposition of the great arteries), it was possible to establish with certainty in all but 1 case which great artery was most directly connected to the systemic venous return.

With a standard single probe echocardiogram, the morphology of the various cardiac structures is inferred mainly from their anteroposterior relation, though some additional subjective evidence can be obtained from their lateral relation. This approach is reliable only when the position of the heart in the chest is normal and when the connections of the various chambers and vessels are also normal. The scarcity of echocardiographic features which unequivocally differentiate intracardiac structures is a serious limitation of the technique in the diagnosis of complex congenital cardiac malformations.

In this report we describe a method for determining which great artery receives most of the systemic venous return, thus improving the accuracy with which we can detect abnormal cardiac connections such as ventriculo-arterial discordance (transposition of the great arteries). The method we describe is valid only when two great arteries and their semilunar valves have been unequivocally identified using standard parasternal echocardiography.

Anatomical considerations

In complex congenital heart disease the relation of the great arteries at their origin from the heart is extremely variable and this relation is frequently independent of their ultimate venous connections. In contrast, the anteroposterior relation of the arch of the aorta to the bifurcation of the pulmonary artery is always constant (*Gray's Anatomy*, 1969). This means that when the great arteries are both visualised with the echocardiographic probe in the suprasternal notch (Goldberg, 1970) the aorta is always closer to the transducer than is the pulmonary artery. If an ultrasonic indicator (for instance 5 per cent dextrose), introduced into the peripheral systemic veins, can be detected when it reaches the great arteries (Valdes-Cruz *et al.*, 1976) then this should allow us to identify whether the pulmonary artery or the aorta is most directly connected to the systemic venous ventricle.

Technique

An intravenous catheter (Longwell 20) is placed in a vein on the dorsum of the hand. The electrocardiographic electrodes are applied and the baby is allowed to settle with a rolled up napkin beneath its shoulders to extend the neck. When the infant is quiet, an echocardiogram is recorded with the transducer placed in the suprasternal notch. The beam is directed posteriorly and somewhat caudally until the echo-free spaces corresponding to the aorta, pulmonary artery, and left atrium are located. To be certain that the beam cuts the arch of the aorta and the bifurcation of the pulmonary artery, no portion of either semilunar valve should be seen. A 1 ml bolus of 5 per cent dextrose is injected rapidly through the cannula during continuous recording of the echocardiogram. We used this technique retrospectively in 6 infants known to have normal ventriculoarterial connections and no significant shunts, and in 6 infants with discordant ventriculoarterial connections (transposition of the great arteries). In the group with normal ventriculoarterial connections only the pulmonary artery opacified (Fig. a). In the group with discordant

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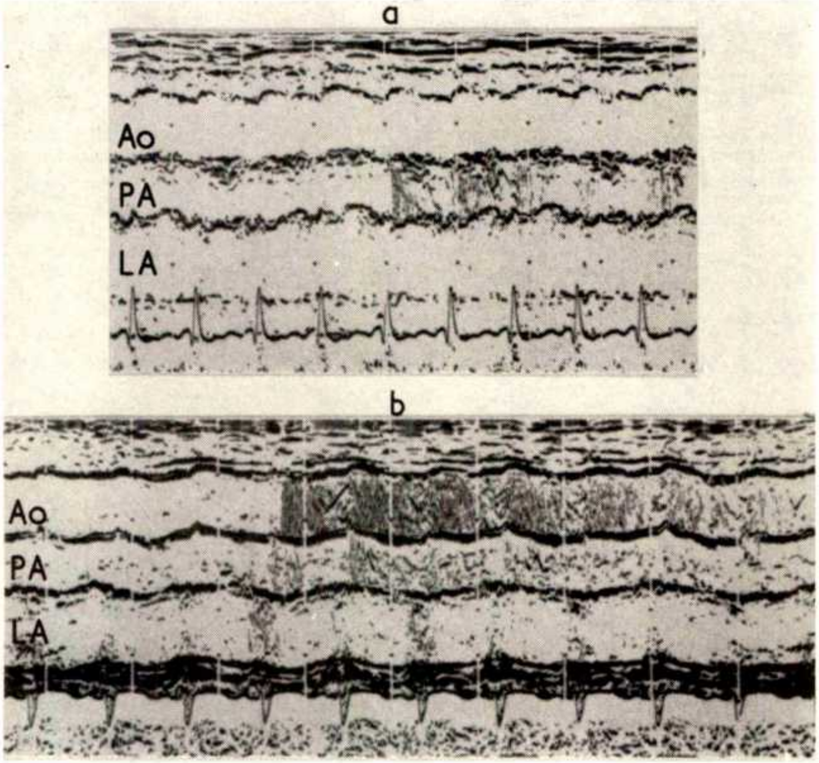

Fig. *(a) This echocardiogram was recorded using the suprasternal approach in a normal infant. The aorta, pulmonary artery, and left atrium are seen. Only the pulmonary artery is opacified after dextrose injection. (b) This echocardiogram is from an infant with transposition of the great arteries after balloon atrial septostomy. It is recorded from the suprasternal approach and shows opacification of both great arteries and the left atrium. The aorta opacifies with greater intensity than the pulmonary artery indicating that it is directly connected to the systemic venous return.*

connections (transposition of the great arteries) both great arteries opacified because of the obligatory bidirectional shunting (Fig. b). In 5 of this group the aortic opacification was more intense than that of the pulmonary artery, correctly identifying the aorta as the great artery most directly connected to the systemic venous return. In the sixth case with discordant ventriculo-arterial connections, a large ventricular septal defect, and free intercirculatory communication, the great arteries were opacified with equal intensity, so that no judgement about venous connections could be made. With this technique we have subsequently correctly predicted the diagnosis of discordant ventriculo-arterial connections (transposition of the great arteries) in one neonate before cardiac catheterisation.

Comment

A major practical problem in neonatal cardiology is deciding which infants need emergency cardiac catheterisation. Standard single probe echocardiography can give valuable information about complex cardiac lesions such as the hypoplastic left heart syndrome (Godman *et al.,* 1974), or primitive ventricle (Mortera *et al.,* 1977). But previously reported echocardiographic criteria for the diagnosis of transposition of the great arteries (Gramiak *et al.,* 1973; Dillon *et al.,* 1973) have not proved absolutely reliable in this age-group. The combination of the suprasternal approach with contrast echocardiography increases our diagnostic precision by identifying patients with discordant ventriculo-arterial connections.

When both great arteries opacify with equal intensity it is impossible to infer the ventriculo-arterial connections. In this situation the decision to catheterise or not must be made using other criteria. However, the method should identify, in the majority of cases, those infants with discordant ventriculo-arterial connections (transposition of the great arteries) with poor intercirculatory mixing, in fact those most in need of an urgent atrial septostomy.

References

Dillon, J. C., Feigenbaum, H., Konecke, L. L., Keutel, J., Hurwitz, R. A., Davis, R. H., and Chang, S. (1973). Echocardiographic manifestations of d-transposition of the great vessels. *American Journal of Cardiology*, **32,** 74–78.

Godman, M. J., Tham, P., and Langford Kidd, B. S. (1974). Echocardiography in the evaluation of cyanotic newborn infant. *British Heart Journal*, **36,** 154–166.

Goldberg, B. B. (1970). Ultrasonic measurement of the aortic arch, right pulmonary artery, and left atrium. *Radiology*, **101,** 383–390.

Gramiak, R., Chung, K. J., Nanda, N., and Manning, J. (1973). Echocardiographic diagnosis of transposition of the great vessels. *Radiology*, **106,** 187–189.

Gray's Anatomy (1969). 34th ed., p. 778. Ed. by D. V. Davies. Longman, Edinburgh.

Mortera, C., Hunter, S., Terry, G., and Tynan, M. (1977). Echocardiography of primitive ventricle. *British Heart Journal*. In the press.

Valdes-Cruz, L. M., Pieroni, D. R., Roland, J. M., and Varghese, P. J. (1976). Echocardiographic detection of intra cardiac right to left shunts following peripheral vein injections. *Circulation*, **54,** 558–562.

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Echocardiography of primitive ventricle

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The angiocardiographic, echocardiographic, and, where available, the necropsy findings were correlated in 32 cases of primitive ventricle. Single probe echocardiography was shown to be a reliable and accurate technique for diagnosis of primitive ventricle; the ventricular and atrioventricular valve appearances were characteristic, and the outlet chamber was usually recognised when present, though it was not possible to say whether it was right or left sided. Abnormalities of the atrioventricular valves were more accurately shown by echocardiography than by angiocardiography though the two techniques were shown to be complementary in the overall diagnostic process.

The introduction of radical surgery for the treatment of univentricular hearts makes accurate anatomical and functional diagnosis essential. The peculiar ability of the echocardiogram to define intracardiac structures, their relations, and their motion, suggests that the technique should play an important role in this diagnostic process. The definitions and terminology used in this paper are those proposed by Anderson and his colleagues (Anderson *et al.*, 1976). Thus the term primitive ventricle is applied to all hearts with absence of the posterior interventricular septum and includes those in which there is atresia of either atrioventricular valve (Quero 1970, 1972).

By correlating echocardiography and angiocardiography and, where available, necropsy material, we have set out to define the value of echocardiography in the assessment of primitive ventricle.

DEFINITIONS

Primitive ventricle

This exists when there is failure of development of the posterior interventricular septum and both atrioventricular valves are in actual or potential communication with the main ventricular chamber (Anderson *et al.*, 1976). When an outlet chamber is present no complete atrioventricular valve annulus is in actual or potential communication with it (Macartney *et al.*, 1976). When a single atrioventricular valve is present it communicates with the main ventricular chamber and no other atrioventricular valve rudiment potentially communicates with the outlet chamber (Anderson and Becker, 1975).

Outlet chamber

This is a chamber with a trabeculated pouch and an infundibular portion; it communicates with the main ventricular chamber but contains neither a complete atrioventricular valve annulus nor the complete tension apparatus of an atrioventricular valve. Echocardiographically its parietal wall moves towards the bulboventricular septum during ventricular systole and no atrioventricular valve is seen completely within its boundaries.

Atrioventricular valve nomenclature

The terms right and left atrioventricular valves are used to avoid confusion. The anatomical right atrioventricular valve is echocardiographically the anterior and the left atrioventricular valve the posterior one. The terms right and left atrioventricular valve are used in this sense throughout.

Connections of great arteries

In primitive ventricle with outlet chamber the great arteries are considered to be normally connected when the aorta arises from the main chamber and the pulmonary artery from the outlet chamber. When the converse is true transposition exists (Shinebourne *et al.*, 1976). When both great arteries arise from one chamber whether an outlet chamber is present or not, this is a double outlet chamber and the term malposition is used irrespective of the anteroposterior relation of the great arteries (Shinebourne *et al.*, 1976). The prefixes d and l

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indicate only the lateral relation of the great arteries and have no specific morphogenetic or diagnostic significance (Carr *et al.*, 1968), though knowledge of these relations is of obvious surgical importance. When a single arterial trunk is present the terminology of Shinebourne *et al.* (1976) is used.

Straddling atrioventricular valves

In the context of primitive ventricle, straddling refers to an atrioventricular valve, part of whose tension apparatus arises in the outlet chamber. This atrioventricular valve then straddles the bulboventricular septum (Anderson *et al.*, 1976). A straddling valve is assigned to the ventricular chamber into which more than 50 per cent of its orifice appears to open. Thus, in primitive ventricle all straddling valves open at least 50 per cent into the main chamber.

Subjects and methods

Echocardiograms were recorded in 32 patients aged from 1 day to 28 years with an angiocardiographic diagnosis of primitive ventricle in 31, necropsy confirmation of the angiocardiographic diagnosis in 4, and necropsy diagnosis only in 1 case in whom angiocardiography was not performed. In all 31 patients who had angiocardiography main chamber ventriculograms were recorded using either biplane Elema or multiple single plane cine projections. Single probe echocardiograms were obtained using a 2·25 MHz transducer focused at 7·5 cm with an Echoview X echocardiograph machine and a Honeywell ultraviolet recorder. In all cases the echocardiographic relations were established using continuous sweeps. In 20 patients the angiograms had been performed before echocardiography but were reviewed by one of us without knowledge of the echocardiographic findings. In 12 the echocardiographic assessment and diagnosis had been made before the angiocardiographic studies.

Main ventricular chamber size and performance were assessed echocardiographically using end-diastolic dimension and the mean rate of internal dimension shortening (mean V_{CF}, respectively (Cooper *et al.*, 1972; Kaye *et al.*, 1975). These data were compared with values for the normal left ventricle (Hunter *et al.*, 1975).

Results

Table 1 shows the final diagnoses of all patients; these diagnoses are a synthesis of all the available data obtained from angiocardiograms, echocardiograms, and necropsies.

Table 1 *Distribution of cases in final diagnosis*

Final diagnosis	*No.*
Primitive ventricle with outlet chamber	30
With 2 atrioventricular valves	17
Normal great arteries	1
Transposition of great arteries (TGA)	16
With 1 atrioventricular valve	13
Right atrioventricular valve atresia with TGA	4
Right atrioventricular valve atresia with normal great arteries	7
Left atrioventricular valve atresia with TGA	1
Left atrioventricular valve atresia with single arterial trunk (aorta)	1
Primitive ventricle without outlet chamber	2
With 2 atrioventricular valves and single arterial trunk (aorta)	1
With single (common) atrioventricular valve and l-malposition	1

Thirty patients had primitive ventricle with an outlet chamber: in 18 this was to the left and anterior, in 11 it was to the right and anterior, and in 1 it was directly anterior to the main chamber. Two patients had no outlet chamber. Eighteen patients had 2 atrioventricular valves, 11 had right atrioventricular valve atresia, 2 had left atrioventricular valve atresia, and 1 had a common atrioventricular valve. Sixteen of the cases with 2 atrioventricular valves had a left-sided outlet chamber and 1 had a right-sided outlet chamber, and 1 had no outlet chamber. Ten of the cases with right atrioventricular valve atresia had a right-sided outlet chamber and 1 had a left-sided outlet chamber. In the 2 cases with left atrioventricular valve atresia the outlet chamber was directly anterior in one and to the left in the other. In 3 cases with 2 atrioventricular valves the right atrioventricular valve straddled the bulboventricular septum.

Transposition of the great arteries was present in 21 cases, normal arterial relation in 8, single arterial trunk (aorta) in 2, l-malposition of the great arteries in 1.

ECHOCARDIOGRAPHY

In 28 of the cases with an outlet chamber its presence was detected by echocardiography as an interior echo free chamber (Fig. 1, 3, and 8). However, it was not possible to say with certainty whether the outlet chamber was to the right or to the left. The septal structure separating the outlet chamber from the main chamber was taken to represent the bulboventricular septum (Felner *et al.*, 1976) because of its abnormal anterior position and because no complete atrioventricular valve was detected in front of it. In no case were there echoes suggesting the presence of a posterior ventricular septum (Assad-Morell *et al.*, 1974; Felner *et al.*, 1976).

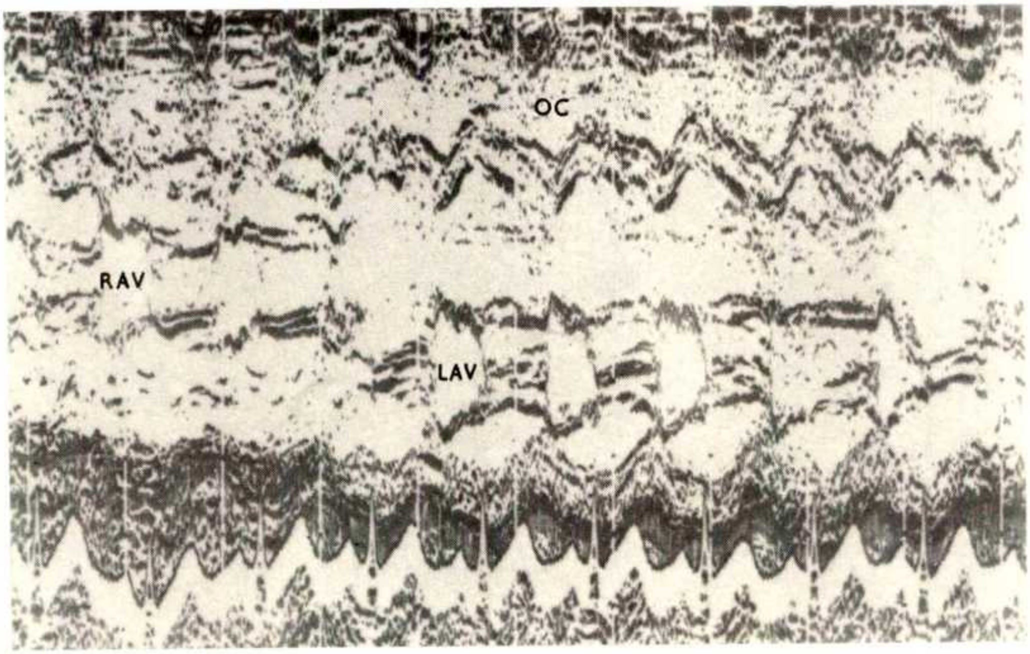

Fig. 1 *This echocardiogram shows an anteriorly placed outlet chamber, the bulboventricular septum and the main ventricular chamber containing two atrioventricular valves. These valves were visualised completely using slight sideways angulation of the probe. The right atrioventricular valve does not show excessive diastolic movement of its posterior cusp. OC, outlet chamber; RAV, right atrioventricular valve; LAV, left atrioventricular valve.*

In all 18 patients with 2 atrioventricular valves, both were detected. In each case, both valves lay within the main ventricular chamber (Fig. 1). In 3 patients part of the anterior cusp of the right atrioventricular valve crossed the bulboventricular septum into the outlet chamber. This was taken to indicate straddling, as the major part of the valve, the posterior cusp, was within the main ventricular chamber (see Fig. 3) (Seward *et al.*, 1975; Lacorte *et al.*, 1976). In all patients with 2 atrioventricular valves, these structures could be seen in the same echocardiographic plane without an intervening septal structure (Felner *et al.*, 1976) (Fig. 2, 3, and 4), and in 13 of them both valves were shown simultaneously (Fig. 2). The diastolic movement of the posterior cusp of the right atrioventricular valve was frequently greater than the diastolic excursion of the anterior cusp (Fig. 2), though this finding was not invariable (Fig. 1). The posterior excursion of the right atrioventricular valve and the anterior excursion of the left atrioventricular valve were such that they overlapped in diastole (Fig. 2 and 3). In one patient the right atrioventricular valve was mobile but hypoplastic and unequivocally communicated with the main ventricular chamber. Diastolic vibration of the left atrioventricular valve was present in 7 cases (Fig. 4).

A single fully mobile atrioventricular valve was detected in 14 cases echocardiographically, but in 11 it was not possible to differentiate a common atrioventricular valve (Fig. 5B) from right or left atrioventricular valve atresia (Fig. 5A and 5C). In the remaining 3 cases a structure was seen whose movement and position suggested that it was a rudimentary atrioventricular valve. In all 3, this rudiment appeared potentially to communicate with the ventricular chamber (Anderson and Becker, 1975; Macartney *et al.*, 1976). In 2 it was anterior to the fully formed atrioventricular valve (Fig. 6), and right atrioventricular valve atresia was shown on angiography. In the third case the rudiment was located posteriorly (Fig. 7) and left atrioventricular valve atresia was confirmed angiocardiographically.

In 30 cases the posterior wall of the posterior great artery or the single arterial trunk and the left atrioventricular valve or single atrioventricular valve appeared echocardiographically to be connected (Fig. 8A). In the 30 cases with an outlet chamber there was no consistent relation between the bulboventricular septum and the anterior wall of the

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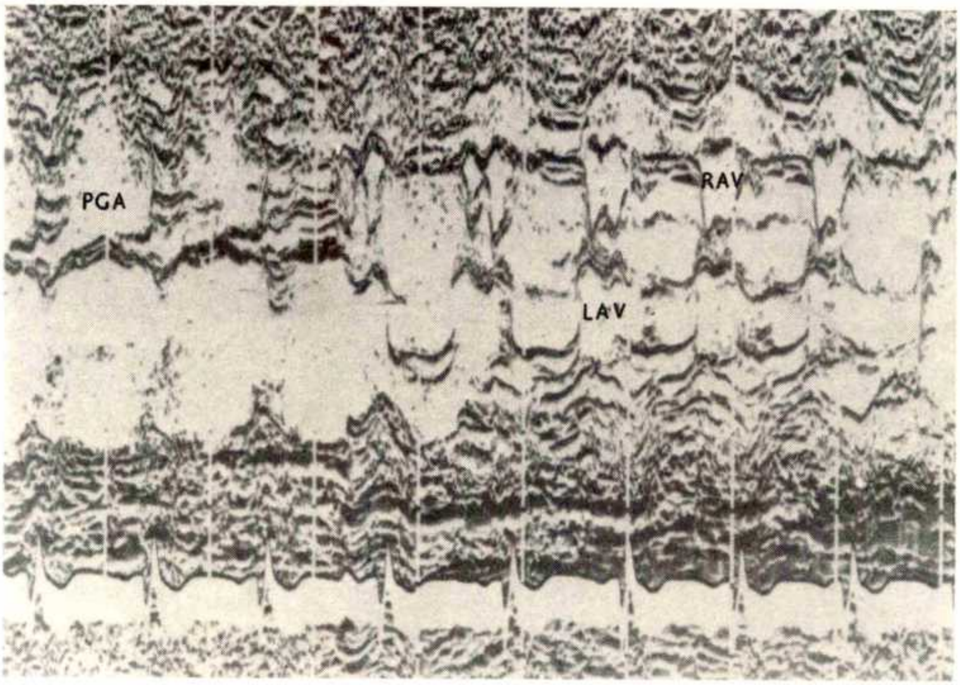

Fig. 2 *In this echocardiogram the transducer has been swept from the posterior great artery down into the main ventricular chamber, within which lie 2 atrioventricular valves. The posterior cusp of the right atrioventricular valve shows excessive posterior diastolic movement. There is no evidence of a posterior ventricular septum and the atrioventricular valves touch in diastole. PGA, posterior great artery; RAV, right atrioventricular valve; LAV, left atrioventricular valve.*

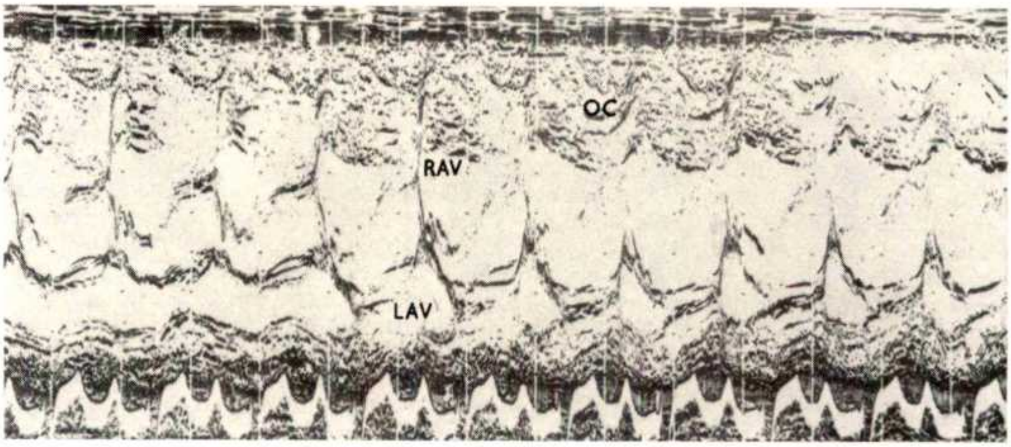

Fig. 3 *This echocardiogram shows 2 atrioventricular valves and an outlet chamber. The left atrioventricular valve lies wholly within the main chamber. The right atrioventricular valve lies mainly within the main chamber but its anterior cusp crosses the bulboventricular septum into the outlet chamber. OC, outlet chamber; RAV, right atrioventricular valve; LAV, left atrioventricular valve.*

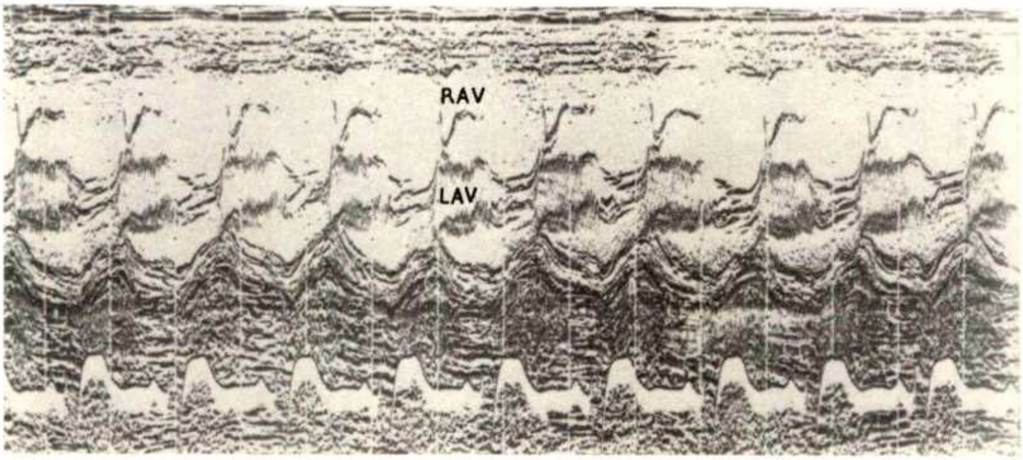

Fig. 4 *This echocardiogram shows 2 atrioventricular valves lying within the main ventricular chamber. The right valve is only partially seen but its posterior cusp touches the anterior cusp of the left valve in diastole. The left valve shows conspicuous fine vibration of both cusps in diastole. RAV, right atrioventricular valve; LAV, left atrioventricular valve.*

posterior great artery (Fig. 8A and 8B). Though the right atrioventricular valve and the posterior great artery were seen frequently at the same echocardiographic depth, we failed to show a consistent pattern of connection between these two structures. In 21 cases 2 great arteries were definitely identified though it was not possible to differentiate aorta from pulmonary artery by echocardiography. In all the other cases only one great artery was definitely seen and in 2 of these the diagnosis by angiocardiography was single arterial trunk (aorta). There was no obvious reason why only one great artery could be identified echocardiographically in the remaining 9 cases. However, 7 of these had right atrioventricular valve atresia with normally related great arteries suggesting that in this variant of primitive ventricle it is difficult to show the anterior great artery echocardiographically.

Echocardiographic estimates of main ventricular chamber size and performance

The dimensions and mean rates of internal di-

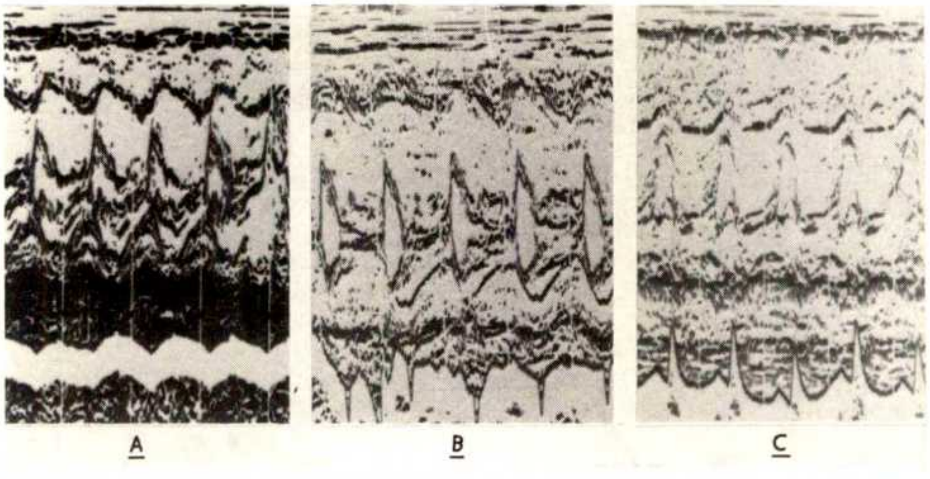

Fig. 5 *This figure shows 3 examples of single atrioventricular valve lying within a primitive ventricle. The appearances are closely similar, and are recorded in (A) a case of right atrioventricular valve atresia; (C) a case of left atrioventricular valve atresia; (B) a case of common atrioventricular valve.*

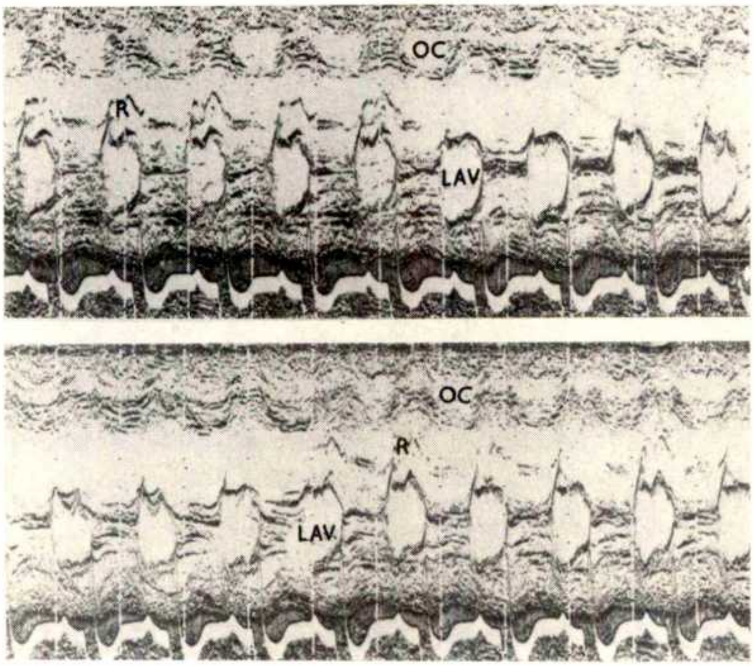

Fig. 6 *A large mobile posterior left atrioventricular valve is seen lying within a primitive ventricle. Anterior to it and within the main ventricular chamber a small less mobile atrioventricular valve structure is seen. Catheterisation and angiocardiography confirmed that this patient had right atrioventricular valve atresia. OC, outlet chamber; LAV, left atrioventricular valve; R, rudimentary right atrioventricular valve.*

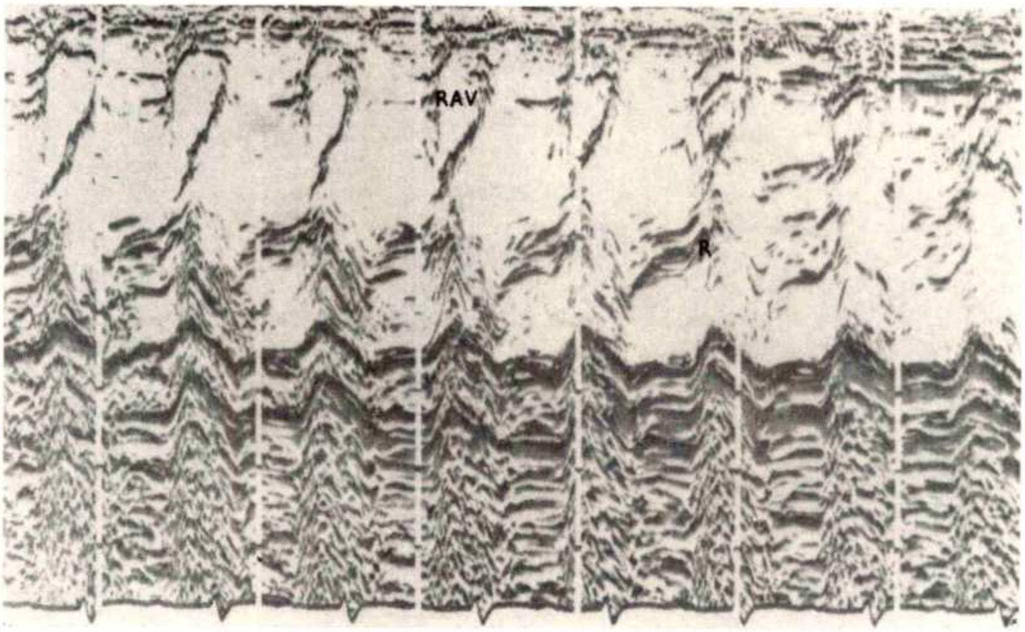

Fig. 7 *This patient was shown by angiocardiography to have primitive ventricle with left atrioventricular valve atresia. The echocardiogram shows a right atrioventricular valve with excessive posterior diastolic excursion. Posteriorly a poorly formed left atrioventricular valve structure is seen within the primitive ventricle and touches the anterior valve in diastole. RAV, right atrioventricular valve; R, rudimentary left atrioventricular valve.*

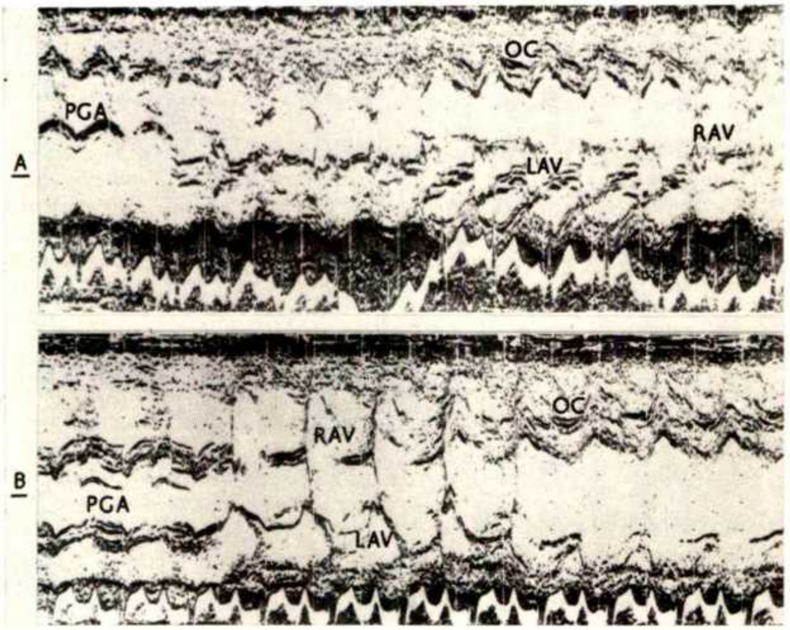

Fig. 8 *These echocardiograms show the variability of the relation between the posterior great artery, the bulboventricular septum, and the left atrioventricular valve. The upper picture (A) shows echocardiographic connection of the posterior wall of the posterior great artery and the left atrioventricular valve. In the lower picture (B) there is straddling of the bulboventricular septum by the right atrioventricular valve. These examples also show the variable relation between the posterior great artery and the right atrioventricular valve. OC, outlet chamber; PGA, posterior great artery; LAV, left atrioventricular valve; RAV, right atrioventricular valve.*

mension shortening are given in Table 2. These measurements were made in 30 of the 32 patients. The end-diastolic dimensions were compared with normal values for the left ventricle obtained from 409 normal subjects and were found to be greater than 2 standard deviations larger than the mean normal for age in 20, greater than 1 standard deviation larger in 5, and less than the mean normal for age in only 1 case. The mean rate of internal dimension shortening was less than $1\cdot0^{-1}$ in 8, but in only 1 case was it less than $0\cdot8^{-1}$. When compared with our normal data, mean V_{CF} was within 2 standard deviations of the mean in 21 patients, more than 2 standard deviations above the mean in 5, and more than 2 standard deviations below the mean in 4.

Discussion

The echocardiographic approach in primitive ventricle does not differ radically from that in other forms of congenital heart disease. The complexity of the lesions encountered necessitates a logical approach to the diagnosis, a picture being built up using continuous sweeps based on structures with recognisable echocardiographic features. After the standard scans have been performed it is possible to show the relations of the atrioventricular valves to each other, to the ventricular cavities, and to the great arteries by appropriate modifications of the angle of sweep. Careful attention to the near gain

Table 2 *Main chamber size and performance*

Cases	*Age*	*EDD (cm)*	*ESD (cm)*	*VCF* (S^{-1})
1	24 h	1·5	0·9	2·5
2	24 h	2·6	1·5	3·0
3	24 h	1·9	1·3	1·4
4	48 h	2·9	2·1	1·4
5	2 m	4·7	3·1	1·48
6	5 m	3·2	1·6	2·8
7	7 m	5·1	3·9	0·8
8	7 m	4·1	3·1	1·0
9	1 y 5 m	4·3	2·8	1·7
10	1 y 11 m	3·3	2·4	1·8
11	2 y	3·5	2·2	2·2
12	5 y	4·4	3·3	1·0
13	5 y	7·2	4·6	1·1
14	5 y	6·0	4·0	1·4
15	5 y	5·0	3·9	1·0
16	7 y	4·9	4·0	0·8
17	7 y	3·2	2·2	1·1
18	8 y	5·6	4·2	0·9
19	9 y	5·3	4·2	0.8
20	10 y	4·6	2·4	1·9
21	10 y	5·3	3·3	1·3
22	11 y	4·9	4·0	0·8
23	11 y	3·6	2·3	1·2
24	12 y	4·7	3·3	1·0
25	13 y	4·8	3·5	0·9
26	14 y	9·0	7·2	0·7
27	15 y	7·0	5·2	1·0
28	18 y	6·3	3·6	1·3
29	20 y	6·8	4·5	1·1
30	28 y	7·8	5·7	0·8

EDD, end-diastolic dimension; ESD, end-systolic dimension; V_{CF}, mean rate of internal dimension shortening.

control is necessary to identify the presence or absence of superficial structures such as the outlet chamber. We emphasise, therefore, that in general no single echocardiographic slice can be diagnostic in congenital heart disease.

Using this approach we have been able to show good agreement between the echocardiographic findings and the anatomical features assessed by angiography and necropsy. Angiography is in general superior to echocardiography in the definition of ventricular anatomy and the ventriculoarterial connections. However, in the examination of the atrioventricular valves, the two methods are complementary. For example, the detection of hypoplastic or atretic atrioventricular valve rudiments is possible with the echocardiogram but, if valve rudiments are not recognised, the angiocardiogram is necessary to decide which atrioventricular valve is atretic. In our group of patients the complementary roles of these two methods are well shown by the finding of a range of right and left atrioventricular valve abnormalities from hypoplasia to rudimentary valve structures in actual or potential communication with the main ventricular chamber, providing further support for the concept of Anderson and Becker (1975) that the majority of cases of 'tricuspid atresia' do in fact have a primitive ventricle with right atrioventricular valve atresia.

The echocardiographic diagnosis of primitive ventricle may be summarised as follows. When there are 2 atrioventricular valves and an outlet chamber the following echocardiographic features are diagnostic: (i) Both atrioventricular valves occupy one ventricular cavity with their diastolic motions overlapping. (ii) There is an anterior chamber showing a ventricular type of free wall motion and containing no atrioventricular valve completely within its boundaries. (iii) There is absence of echoes suggesting a posterior interventricular septum. Additionally the posterior diastolic motion of the right atrioventricular valve may appear to be excessive but this is by no means a universal finding. If no outlet chamber is present the demonstration of criteria (i) and (iii) is strongly suggestive of the diagnosis of primitive ventricle.

If only 1 atrioventricular valve is present then the demonstration of an outlet chamber as defined above is strongly suggestive but not diagnostic. If, however, rudiments of an atretic valve potentially communicating with the main chamber are found, then this together with criteria (ii) and (iii) is diagnostic. When one atrioventricular valve is shown but no echoes are seen from an outlet chamber or atretic valve rudiments, then the diagnosis cannot be made with certainty by echocardiography alone.

These diagnostic criteria may appear rather cautious but suggestive evidence such as the increased excursion of the posterior cusp of the right atrioventricular valve may be misleading because a wide range of atrioventricular valve amplitude of motion can be seen in primitive ventricle. Furthermore, negative echocardiographic findings such as the absence of posterior septal echoes or the absence of atrioventricular valve echoes in the outlet chamber are potentially misleading when taken in isolation.

Straddling of the right atrioventricular valve appears to occur more frequently in association with primitive ventricle (Anderson *et al.*, 1976) than with other abnormalities (Liberthson *et al.*, 1971). Thus, if echocardiographic straddling of this valve is demonstrated, primitive ventricle must be definitely excluded before an alternative diagnosis is made. In our experience, however, in the presence of straddling right atrioventricular valve, there still exists an area of diagnostic difficulty between primitive ventricle and other conditions associated with straddling, e.g. transposition of the great arteries with ventricular septal defect (Liberthson *et al.*, 1971). Though valuable clinical information about the ventriculoarterial connections and the great arteries can be obtained echocardiographically, this information is not essential for the diagnosis of primitive ventricle which depends on examination of the intraventricular structures. Furthermore, angiocardiography can still more reliably define ventriculoarterial connections.

Not surprisingly the majority of patients in this series had main ventricular chamber end diastolic dimensions which were considerably larger than the normal left ventricular dimensions. In spite of this, the performance of the main chamber was found to be at least comparable to that of the normal left ventricle in the majority of cases, and in none was severely impaired.

In the diagnosis of primitive ventricle, as in other forms of complex congenital heart disease, echocardiography does not supplant or replace cardiac catheterisation and angiocardiography. However, it has a very valuable part to play in the overall diagnostic process. Echocardiograms provide information about atrioventricular valve structure and function, which is more accurately and easily obtained in this way than by other techniques. In addition, information about the performance of the main ventricular chamber may well be of great importance in the preoperative assessment of primitive ventricle (F. Fontan, 1976, personal communication).

References

Anderson, R. H., and Becker, A. E. (1975). Morphological observations in specimens of tricuspid atresia with reference to bulbo-ventricular morphogenesis (abstract). *British Heart Journal*, **37**, 552.

Anderson, R. H., Becker, A. E., Wilkinson, J. L., and Gerlis, L. M. (1976). Morphogenesis of univentricular hearts. *British Heart Journal*, **38**, 558–572.

Assad-Morell, J. L., Tajik, A. J., and Giuliani, E. R. (1974). Echocardiographic analysis of the ventricular septum. *Progress in Cardiovascular Diseases*, **17**, 219–237.

Carr, I., Tynan, M., Aberdeen, E., Bonham-Carter, R. E., Graham, G., and Waterston, D. J. (1968). Predictive accuracy of the 'loop-rule' in 109 children with classical complete transposition of the great arteries. *Circulation*, **37–38**, Suppl. VI, 52.

Cooper, R. H., O'Rourke, R. A., Karliner, J. S., Peterson, K. L., and Leopold, G. R. (1972). Comparison of ultrasound and cineangiographic measurements of the mean rate of circumferential fiber shortening in man. *Circulation*, **46**, 914–923.

Felner, J. M., Brewer, D. B., and Franch, R. H. (1976). Echocardiographic manifestations of single ventricle. *American Journal of Cardiology*, **38**, 80–84.

Hunter, S., Mortera, C., Sheridan, D., and Tynan, M. (1975). Age related changes in left ventricular size and performance, an echocardiographic study (abstract). *Circulation*, **51–52**, II-198.

Kaye, H. H., Tynan, M., and Hunter, S. (1975). Validity of echocardiographic estimates of left ventricular size and performance in infants and children. *British Heart Journal*, **37**, 371–375.

Lacorte, M. A., Fellows, K. E., and Williams, R. G. (1976). Overriding tricuspid valve: echocardiographic and angiocardiographic features. *American Journal of Cardiology*, **37**, 911–919.

Liberthson, R. R., Paul, M. H., Muster, A. J., Arcilla, R. A., Eckner, F. A. O., and Lev, M. (1971). Straddling and displaced abnormalities, orifices and valves with primitive ventricle. *Circulation*, **43**, 213–226.

Macartney, F. J., Partridge, J. B., Scott, O., and Deverall, P. D. (1976). Common or single ventricle, and angiocardiographic and hemodynamic study of 42 patients. *Circulation*, **53**, 543–554.

Quero, M. (1970). Atresia of the left atrioventricular orifice associated with a Holmes heart. *Circulation*, **42**, 739–744.

Quero, M. (1972). Coexistence of single ventricle with atresia of one atrioventricular orifice. *Circulation*, **46**, 794–798.

Seward, J. B., Tajik, A. J., and Ritter, D. G. (1975). Echocardiographic features of straddling tricuspid valve. *Mayo Clinic Proceedings*, **50**, 427–434.

Shinebourne, E. A., Macartney, F. J., and Anderson, R. H. (1976). Sequential chamber localization—logical approach to diagnosis in congenital heart disease. *British Heart Journal*, **38**, 327–340.

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British Heart Journal, 1977, **39**, 856–859

What should we call the 'crista'?

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Review of published work concerning congenital cardiac anomalies reveals that at least four different structures have been described as the crista supraventricularis, in addition to the structure which in the normally formed right ventricle separates pulmonary and tricuspid valves. Possibility of further confusion arises since at least two different structures have been described under the name 'septal band'. We suggest that this potentially confusing situation will be best resolved by reserving the term 'crista' for description of the muscle mass between inflow and outflow portions of the right ventricle when there are no additional outflow tract anomalies. We then suggest that at least three separate structures warrant description in hearts with outflow tract anomalies. The first separates the semilunar valves, the second separates a semilunar valve from an atrioventricular valve, and the third is an extensive septal trabeculation of the right ventricle. Our suggested terms for these structures are the infundibular septum, ventriculo-infundibular fold, and trabecula septomarginalis, respectively. However, we believe that such terms would be better decided and agreed upon within an internationally formulated 'Nomina Cardiologica', a terminology as yet lacking in congenital heart disease.

Many of the controversies in paediatric cardiology relate not so much to differing observations as to differing interpretations of the embryological derivation of structures, and hence to usage of different names to describe these structures. 'Crista supraventricularis' is among the most abused of such names. Introduced by Wolff (1781) to describe the structure which separates pulmonary and tricuspid valves in the normal right ventricle, the term 'crista' has been applied to at least four different muscular structures related to the outflow tracts of congenitally malformed hearts (Fig. 1). The confusion produced by such usage is compounded by the fact that other terms have been used to describe these structures by other investigators, and in several instances the same name has been applied to different structures by different workers. Our present purpose is to make a plea for uniformity, and thus attempt to avoid such differences in usage by future workers who study congenitally malformed hearts. We accept that achievement of such uniformity will be difficult if not impossible. None the less, we suggest that the first step in achieving such uniformity will be the reservation of the term 'crista' for description of the supraventricular muscle mass of the *normal* right ventricle, as indeed it was initially intended. We have previously argued at length why we believe this to be necessary (Becker *et al.*, 1975; Shinebourne *et al.*, 1975), and similar arguments have been advanced by Goor and Lillehei (1975). If 'crista' is discarded in other contexts, we believe the next essential step will be to define any structures worthy of description in *anatomical* terms alone, without reference to embryological interpretation.

In our opinion, in all hearts with malformations of the outflow tracts, at least three muscular structures always warrant definition and description. The first is a muscle bundle which, in anatomical terms, separates the two semilunar valves, whatever the ventricular origin of these valves. The second is, again in anatomical terms, a muscular structure which separates a semilunar from an atrioventricular valve, whether these valves are in the morphologically right or left ventricles or in a primitive (single) ventricle. The third and final structure is a prominent septal trabeculation which is one of the anatomical features of the morphologically right ventricle. It can rightly be argued that when defined in such terms it matters little what the structures

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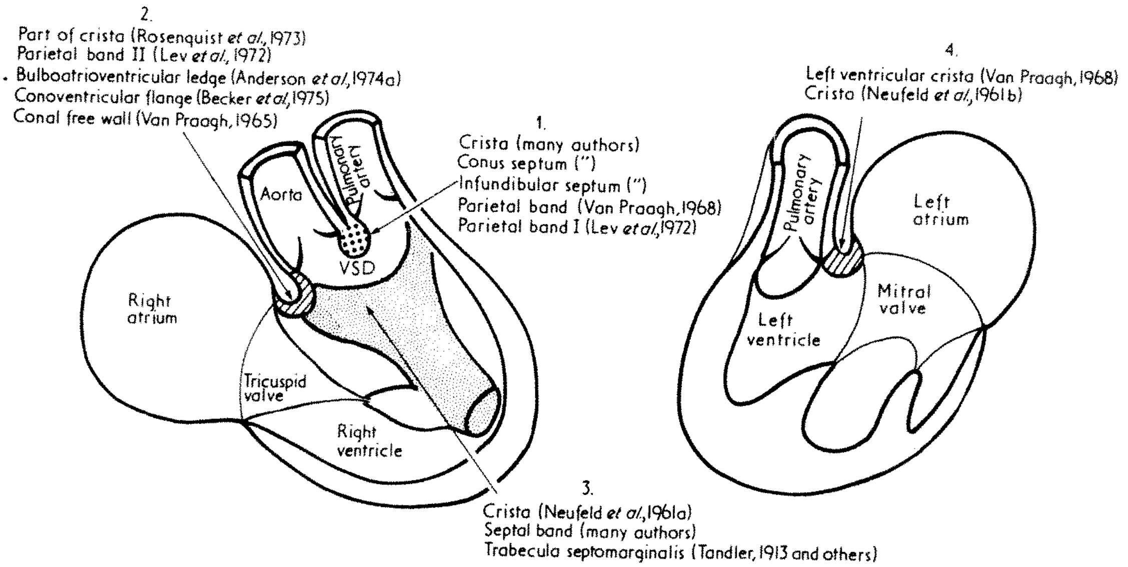
2.
Part of crista (Rosenquist *et al*, 1973)
Parietal band II (Lev *et al*, 1972)
Bulboatrioventricular ledge (Anderson *et al*, 1974a)
Conoventricular flange (Becker *et al*, 1975)
Conal free wall (Van Praagh, 1965)
Aorta
Pulmonary artery
VSD
1.
Crista (many authors)
Conus septum (")
Infundibular septum (")
Parietal band (Van Praagh, 1968)
Parietal band I (Lev *et al*, 1972)
Right atrium
Tricuspid valve
Right ventricle
3.
Crista (Neufeld *et al*, 1961a)
Septal band (many authors)
Trabecula septomarginalis (Tandler, 1913 and others)
4.
Left ventricular crista (Van Praagh, 1968)
Crista (Neufeld *et al*, 1961b)
Pulmonary artery
Left atrium
Mitral valve
Left ventricle

Fig. 1 *Diagrammatic representation of hypothetical hearts to illustrate the structures which, by different investigators at different times, have been termed the crista supraventricularis, or described as part of the 'crista'. The diagram on the left illustrates a hypothetical double outlet right ventricle. The ventricular septal defect is shown beneath both semilunar valves, since it bears a similar relation to whichever great artery is above it. The diagram on the right illustrates a hypothetical case of overriding pulmonary artery with muscular tissue between the pulmonary and mitral valves. The references are chosen only as illustrative examples, and are in no way to be construed as an exhaustive catalogue or as indicating precedence of description.*

are called, since if each investigator carefully defines his terms, all will be able to comprehend his nomenclature. However, we contend that it is self evident that uniformity of nomenclature of anatomical structures in normal and anomalous postnatal hearts will considerably facilitate both mutual understanding and communication.

If such a uniform nomenclature is to satisfy our second suggested criterion and eschew embryological considerations, we submit it must *not* use the term 'conus' (Van Mierop, 1974). For this reason, some of us are forced to change our nomenclature, which has hitherto employed the term 'conus' extensively (Becker *et al.*, 1975; Shinebourne *et al.*, 1975). It can be argued that nomenclature should be changed only if the previous nomenclature is either inaccurate or unsatisfactory. We submit that this is indeed the case with 'conus'. The term is used to describe different parts of the embryonic heart by different investigators (Goor and Lillenhei, 1975). As used by Goor and Lillehei (1975), the 'conus' seems to be interchangeable with the time-honoured 'infundibulum', as is indeed indicated by these authors. However, Goor (1972) had earlier reacted strongly against a suggestion by Lev (1972) that 'infundibulum' be substituted for 'conus'. In contrast to this usage, Van Praagh and Van Praagh (1965) specifically argued that the 'conus' was *not* to be considered as a cylinder of musculature (p. 420). Further difficulties arise from usage of 'conus' which derive from embryological interpretations. Goor and Lillehei (1975) argued that the embryonic conus septum became infiltrated by musculature in the normal heart, and formed the entirety of the normal crista supraventricularis. This is in contrast to our own observations (Anderson *et al.*, 1974a, b; Van Mierop, 1974). Furthermore, they argued that in truncus specimens, a ridge of tissue adjacent to the atrioventricular valve was a remnant of the conus septum, while agreeing with the concept of Van Praagh and Van Praagh (1965) that truncus hearts with tricuspid semilunar valves resulted from lack of growth of the subpulmonary conus. This seems an inconsistent argument and underlines the necessity for our second requirement, that of avoiding embryological interpretations when naming structures in anomalous hearts. From these considerations it follows that the term 'conus' *must* be discarded in descriptions of postnatal, or fully developed hearts. We further suggest that Lev's (1972) advice be followed, and the term 'infundibulum' be substituted for 'conus', as in the recent study of English (1976). This use of 'infundibulum' makes it easy to name the first two of the three structures described above. Thus, the structure which interposes between two semilunar valves can be described as the *infundibular septum* (Fig. 2). In malformed hearts this septum usually has a body, a septal insertion, and a parietal insertion. Any muscular structure which in an anomalous heart separates the semilunar from the atrioventricular valves can be termed the *ventriculo-infundibular fold* (Fig. 2). This term is applicable whether the fold exists in a right, a left, or a primitive ventricle. If this fold is attenuated, then fibrous continuity will exist between semilunar and atrioventricular valves. Though the structure frequently appears as a bar of muscle, transection in a specimen will show that it is a reduplication of the inner curve of the heart wall (Becker *et al.*, 1975). For this reason, 'fold' is a better term than 'flange'.

Naming of the third structure defined above is not made any easier by usage of 'infundibulum'. This is an extensive septal trabeculation seen only in the morphologically right ventricle; it both reinforces the anteroinferior border of many septal defects and supports the tricuspid valve via the medial and anterior papillary muscles which arise directly from the trabecula. The term 'septal band' is widely applied to this structure and has good pedigree (Keith, 1909). However, confusion can arise in clinical usage between the 'septal band' as thus defined and the septal insertion of the infundibular septum, which was termed the 'septal band' by Kjellberg *et al.* (1959) in hearts with Fallot's tetralogy. It is for this reason that we prefer the term *trabecula septomarginalis* for the former (Van Mierop *et al.*, 1963; Becker *et al.*, 1975; Shinebourne *et al.*, 1975). We accept that this term as used by anatomists describes only the moderator band (International Anatomical Nomenclature Committee, 1966). None the less, Tandler (1913) described how, in occasional normal specimens, the trabecular structure could be identified running up towards the crista, and in such normal hearts used 'trabecula septomarginalis' to describe the entire complex. We believe that this occurrence is the rule rather than the exception, and therefore use the term 'trabecula septomarginalis', believing it to be more explicit and less confusing than 'septal band'.

Thus, in conclusion, we submit that the term 'crista supraventricularis' should be used only in the description of hearts with normal right ventricular outflow tracts, without anomalies which derange the alignment of the outflow musculature. Ideally, any substituted nomenclature for description of the supraventricular structures existing in malformed hearts should be agreed in an International document similar to the *Nomina Anatomica*.

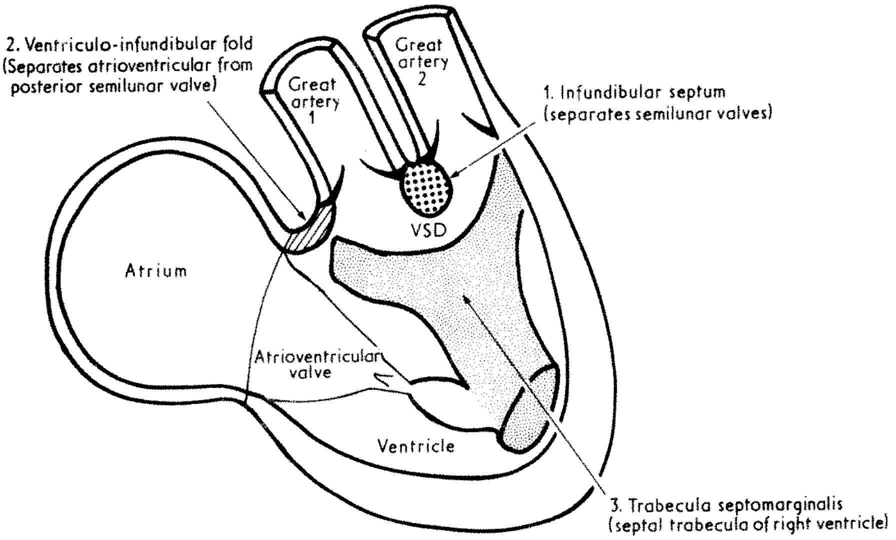
2. Ventriculo-infundibular fold
(Separates atrioventricular from
posterior semilunar valve)
Great
artery
1
Great
artery
2
1. Infundibular septum
(separates semilunar valves)
VSD
Atrium
Atrioventricular
valve
Ventricle
3. Trabecula septomarginalis
(septal trabecula of right ventricle)

Fig. 2 *Diagrammatic representation of suggested terms of muscular structures herein defined. Definitions of structures 1 and 2 are applicable whichever ventricle supports the valve or valves. The structures are illustrated in a diagrammatic right ventricle, however, since structure 3 is one of the distinguishing morphological features of the right ventricle.*

Until such a 'Nomina Cardiologica' is formulated, we suggest that any structure requiring description is first defined and then named using *anatomical* terms, avoiding all interpretations of supposed embryology. We have proposed our own terms using such criteria and present them in the hope that they will stimulate discussion and lead to the formulation of a 'Nomina Cardiologica'.

References

Anderson, R. H., Wilkinson, J. L., Arnold, R., and Lubkiewicz, K. (1974a). Morphogenesis of bulboventricular malformations. I. Consideration of embryogenesis in the normal heart. *British Heart Journal,* **36,** 242–255.

Anderson, R. H., Wilkinson, J. L., Arnold, R., Becker, A. E., and Lubkiewicz, K. (1974b). Morphogenesis of bulboventricular malformations. II. Observations on malformed hearts. *British Heart Journal,* **36,** 948–970.

Becker, A. E., Connor, M., and Anderson, R. H. (1975). Tetralogy of Fallot. A morphometric and geometric study. *American Journal of Cardiology,* **35,** 402–412.

English, T. A. H. (1976). The outflow tract and pulmonary arteries in Fallot's tetralogy and pulmonary atresia with ventricular septal defect. In *Surgery of the Heart,* p. 85. Ed. by J. A. Dyde and R. E. Smith. Plenum, New York.

Goor, D. A. (1972). The conotruncus: I. Its normal inversion and conus absorption. (Correspondence.) *Circulation,* **46,** 635.

Goor, D. A., and Lillehei, C. W. (1975). *Congenital Malformations of the Heart. Embryology, Anatomy and Operative Considerations.* Grune and Stratton, New York.

International Anatomical Nomenclature Committee (1966). *Nomina Anatomica,* 3rd ed. Excerpta Medica, Amsterdam.

Keith, A. (1909). The Hunterian Lectures on malformations of the heart. *Lancet,* **2,** 359–363, 433–435, and 519–523.

Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B. (1959). *Diagnosis of Congenital Heart Disease,* 2nd ed. Year Book Medical Publishers, Chicago.

Lev, M. (1972). The conotruncus: I. Its normal inversion and conus absorption. (Correspondence.) *Circulation,* **46,** 634–635.

Lev, M., Bharati, S., Meng, C. C. L., Liberthson, R. R., Paul, M. H., and Idriss, F. (1972). A concept of double outlet right ventricle. *Journal of Thoracic and Cardiovascular Surgery,* **64,** 271–281.

Neufeld, H. N., DuShane, J. W., and Edwards, J. E. (1961a). Origin of both great vessels from the right ventricle. II. With pulmonary stenosis. *Circulation,* **23,** 603–612.

Neufeld, H. N., DuShane, J. W., Wood, E. H., Kirklin, J. W., and Edwards, J. E. (1961b). Origin of both great vessels from the right ventricle. I. Without pulmonary stenosis. *Circulation,* **23,** 399–412.

Rosenquist, G. C., Sweeney, L. J., Stemple, D. R., Christianson, S. D., and Rowe, R. D. (1973). Ventricular septal defect in tetralogy of Fallot. *American Journal of Cardiology,* **31,** 749–754.

Shinebourne, E. A., Anderson, R. H., and Bowyer, J. J. (1975). Variations in clinical presentation of Fallot's tetralogy in infancy—angiographic and pathogenetic implications. *British Heart Journal,* **37,** 946–955.

Tandler, J. (1913). *Anatomie des Herzens,* p. 64. Gustav Fischer, Jena.

Van Mierop, L. H. S. (1974). Anatomy and embryology of the right ventricle. In *The Heart,* pp. 1–16. Ed. by J. E. Edwards, M. Lev, and M. R. Abell. Williams and Wilkins, Baltimore.

Van Mierop, L. H. S., Alley, R. D., Kausel, H. W., and Stranahan, A. (1963). Pathogenesis of transposition complexes. I. Embryology of the ventricles and great arteries. *American Journal of Cardiology,* **12,** 216–225.

Van Praagh, R. (1968). What is the Taussig-Bing malformation? *Circulation,* **38,** 445–449.

Van Praagh, R., and Van Praagh, S. (1965). The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. *American Journal of Cardiology,* **16,** 406–425.

Wolff, C. F. (1781). Acta Academiae Scientiarum Imperialis Petropolitanae. (Cited by Tandler, 1913.)

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Normal internal calibres of ostia of great arteries and of aortic isthmus in infants and children[1]

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In order to obtain reference data, useful in paediatric cardiology and paediatric cardiovascular surgery, internal diameters of the ostia of the great arteries, of the aortic isthmus, and of the descending aorta were determined with the aid of calibrated probes in 46 necropsy specimens of normal hearts with great vessels. Age range was from 25 weeks of gestational age up to 9 years post partum. *The method used proved to be as accurate as echocardiography* in vivo. *The data revealed linear correlations between body length and calibres of aortic and pulmonary ostia. The correlation between the calibres of the pulmonary and the aortic ostia was also a linear one with the pulmonary ostium being slightly larger than the aortic ostium. From the cross-sectional areas of the aortic isthmus and of the descending aorta an isthmus index was calculated which indicates the presence (and degree) or absence of a narrowing (tubular hypoplasia) of the aortic isthmus. Results show that narrowing of the aortic isthmus is inconstantly present in infants younger than 10 weeks, whereas it is always absent in infants and children older than 10 weeks. No dependence of narrowing of the aortic isthmus on developmental age attained at birth has been found.*

A previous paper (van Meurs-van Woezik and Klein, 1974) confirmed that in congenitally abnormal circulatory conditions, just as in the normal situation, the cross-sectional areas of the ostia of the heart and of the great arteries at different sites correspond to the blood flow through the relevant vessels (Krediet, 1962, 1963, 1965; May, 1968). Clinical methods of quantifying ostial calibres or valve areas (Gorlin and Gorlin, 1951; Yang *et al.*, 1972) have been estimated to be liable to errors as great as 20 to 40 per cent (Rodrigo and Snellen, 1953). Echocardiographic measurements are an exception to this general criticism. Hitherto, however, most of such determinations have been made in older children and adults with evidence of cardiovascular disturbances. When cardiovascular surgery during childhood is considered, one needs reference data on normal infants and children. This paper presents data of such type.

Subjects and method

The material obtained at necropsy consisted of 46

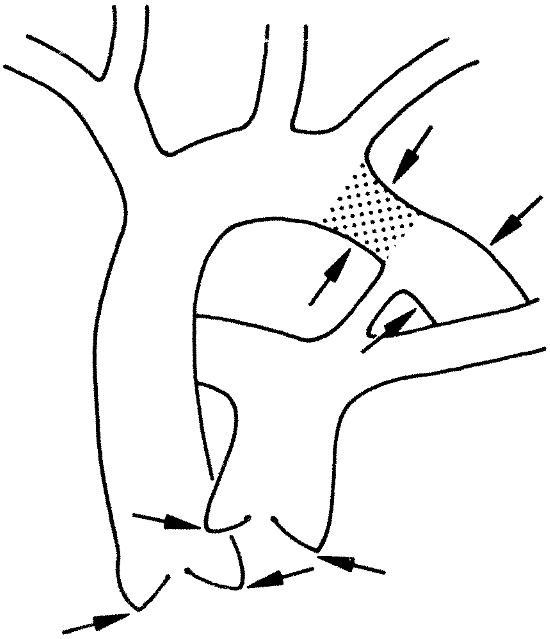

Fig. 1 *Sites of measurements used (arrows); dotted area indicates aortic isthmus (for definition see 'subjects and method').*

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hearts with great vessels from babies and children or from 25 weeks of gestational age up to 9 years after birth. The sex distribution was: male 32, female 11, unknown 3 cases. All specimens were considered normal since cardiovascular abnormalities had not been diagnosed, either clinically or at necropsy. Twenty-one specimens were derived from infants and children who had been born at term, 23 from babies born prematurely, and 2 from immature babies (Table; for definition of premature and immature, see Kloosterman, 1973).

Measurements were performed as described previously on fresh material using a range of calibrated probes differing 1 mm in diameter (van Meurs-van Woezik and Klein, 1974). Diameter values of 0·5 mm were ascertained by interpolation. Measurements were carried out at various sites; those used in the present study are shown in Fig. 1. Ostia were measured at the level of the valve annulus.

The aortic isthmus was defined as the part of the aortic arch between the origin of the left subclavian artery and the mouth of the ductus arteriosus or the insertion of the ligamentum arteriosum.

Table *Synopsis of data on internal calibres of ostia and arteries, body length, body weight, isthmus indices, and of grouping (see 'observations')*

Case No.	*Body length (cm)*	*Body weight (g)*	*Age after birth*		*Gestational age at birth (w)*	*Sex*	*Diameter of ostium (mm)*		*Diameter (mm)*			*Isthmus index*	*Group*
			m	*d*			*Aorta*	*Pulm.*	*Aortic isthmus*	*Aorta desc.*	*Ductus arter.*		
1	30	1100	—	0	25	?	4	4·5	2	3	2·5	0·44	I
2	38	1080	—	2½	28	♀	5	6	3	4	2·5	0·56	I
3	41	1300	—	2	30	♂	6	6·5	4·5	4·5	2·5	1·00	II
4	41	1500	—	6	30⅓	♂	6	8	5	5	4	1·00	II
5	42	1450	—	6	30	?	6	7	4	4·5	2	0·80	I
6	44	1410	—	0	32½	♂	6	7·5	3·5	5	5	0·48	I
7	44	1800	—	0	33	♂	7	7	6	6	5	1·00	II
8	44	1490	—	8	31	♀	6·5	6·5	4·5	5·5	2·5	0·67	I
9	44	1790	1	4	27½	♀	6	7	3	4·5	0·5	0·45	I
10	45	1950	—	1	31	♂	6·5	6	4	6	4	0·44	I
11	45	1425	—	2	29	♂	5·5	5·5	4	4	3	1·00	II
12	45	2240	—	2	42	♂	6·5	7·5	3·5	4·5	2	0·60	I
13	45	1740	—	11	31	♂	6	6	4	4	1·5	1·00	II
14	45	1950	1	—	Prem.	♂	7	7	4	5	2	0·64	I
15	46	2071	—	0	36½	♂	6	7	3·5	6	4·5	0·33	I
16	46	2100	—	1	35½	♂	6	6·5	2·5	5	4	0·24	I
17	46	1825	—	6	36	?	5	6·5	3	5	2	0·36	I
18	48	2340	—	7	32–36	♂	6·5	8	4	5	3	0·64	I
19	49	3050	—	0	Mat.	♀	6·5	7·5	4	5·5	3	0·53	I
20	49	2400	—	3	34½	♀	7	7	4	5·5	4	0·53	I
21	50	2330	—	¾	34	♂	7	8	6	6	3	1·00	II
22	50	3170	—	20	39	♂	7	6·5	5	6	1	0·70	I
23	50	1990	—	29	35	♂	7	8	5·5	5·5	1	1·00	II
24	50	3700	2	—	36	♂	9	10	6	6·5	2	0·85	II
25	51	2490	—	18	Prem.	♀	8	10	6	7	3	0·73	I
26	51	1900	—	23	34	♀	7	7·5	4·5	6	3	0·56	I
27	52	2900	—	5	40	♂	7·5	8	5	6	6	0·70	I
28	52	2950	4	8	32	♀	7	8·5	5	5	0	1·00	III
29	53	3700	—	1	Mat.	♂	9	10	8	9	7	0·79	I
30	53	3100	—	24	38	♀	7·5	8·5	5·5	6	2·5	0·84	II
31	53	3150	4	1	Mat.	♂	9	11	7	6·5	0	1·17	III
32	57	2470	—	20	37	♂	7	8·5	6	6	0	1·00	III
33	57	3780	3	17	32	♂	8·5	9	6·5	6·5	0	1·00	III
34	58	3300	—	13	40	♂	8	8·5	4	5·5	2	0·53	I
35	63	6290	4	9	Mat.	♂	10	10·5	6·5	6·5	0	1·00	III
36	65	4700	2	8	40	♀	9	10	7	8	2·5	0·77	I
37	70	7500	5	25	Mat.	♂	11	11	9	8·5	0	1·12	III
38	74	8100	9	28	Mat.	♂	10·5	12	8	8	0	1·00	III
39	79	9900	10	6	Mat.	♂	12·5	15	8·5	8	0	1·13	III
			y	*m*									
40	90	10 100	1	11	Mat.	♂	11	11	?	?	0	?	?
41	116	16 000	3	9	Mat.	♂	15	17	14	14	0	1·00	III
42	117	19 000	6	9	Mat.	♀	15	18	14	13	0	1·16	III
43	122	?	5	11	Mat.	♂	18	19·5	13·5	13·5	0	1·00	III
44	122	21 000	9	11	Mat.	♂	17	22	14	14	0	1·00	III
45	123	38 000	5	8	Mat.	♂	17	20	12	12	0	1·00	III
46	143	36 000	8	—	Mat.	♂	16·5	18	11·5	10·5	0	1·20	III

Abbreviations: Mat., mature; Prem., premature; ? (unknown) indicates incomplete data or incomplete necropsy specimen.

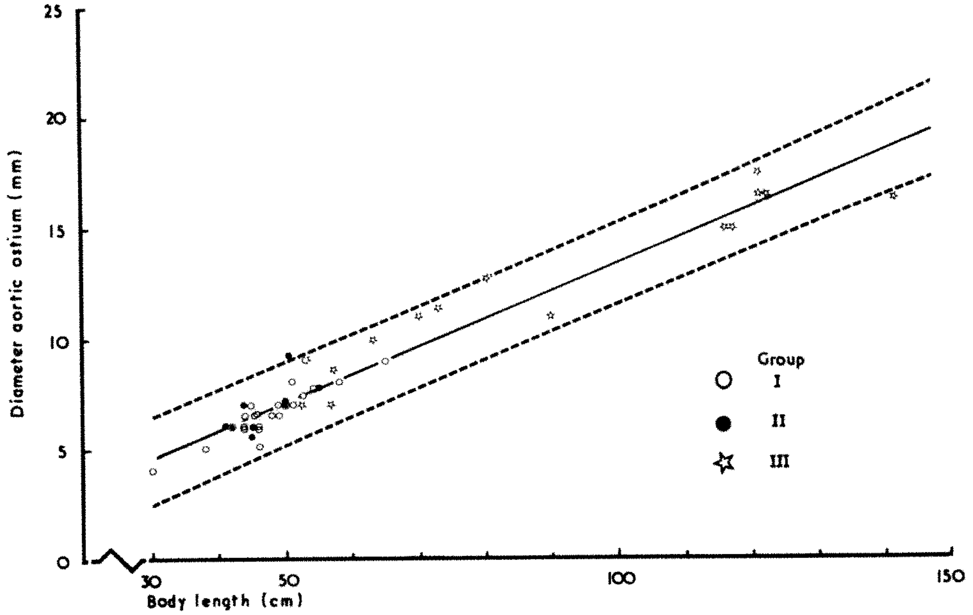

Fig. 2 *Correlation between internal diameters of aortic ostium and body length; interrupted lines indicate prediction interval. For definitions of groups see 'observations' and Table.*

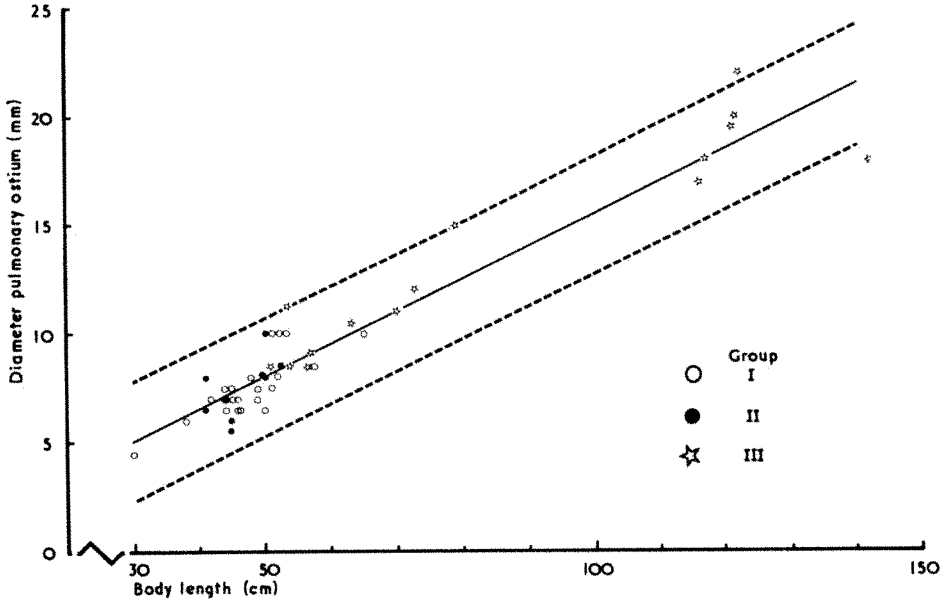

Fig. 3 *Correlation between internal diameters of pulmonary ostium and body length; interrupted lines indicate prediction interval. For definitions of groups see 'observations' and Table.*

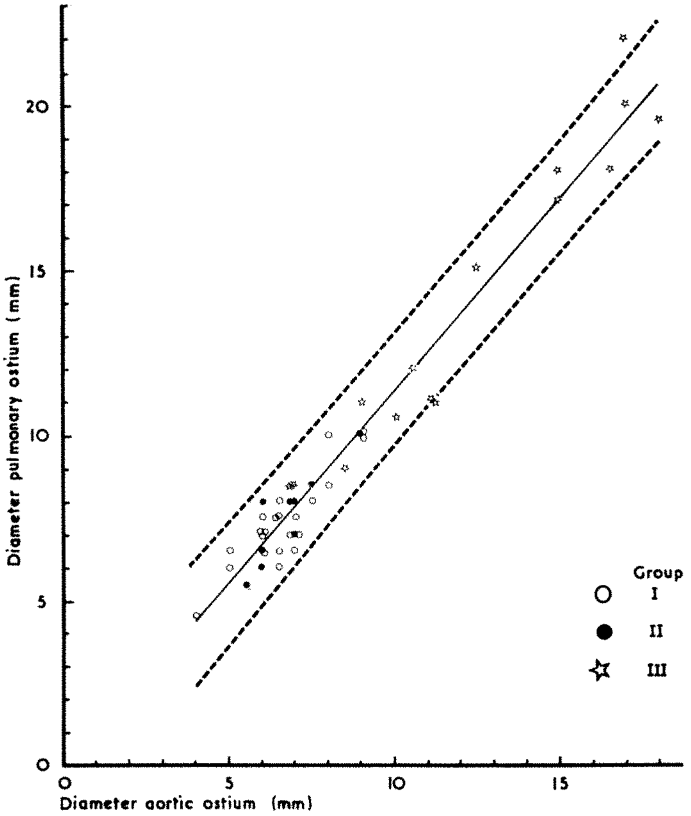

Fig. 4 *Correlation between internal diameters of aortic and pulmonary ostia; interrupted lines indicate prediction interval. For definitions of groups see 'observations' and Table.*

Cross-sectional areas of the ostia of the great arteries, of the aortic isthmus, and of the descending aorta were calculated as an indication of blood flow. Correlations were calculated following Sachs (1973).

Observations

In the Table the data on internal measurements of ostia and arteries, on body length, body weight, and age are summarised. In three graphs the following relations are depicted: diameters of aortic ostia versus body length (Fig. 2), diameters of pulmonary ostia versus body length (Fig. 3), diameters of pulmonary ostia versus diameters of aortic ostia (Fig. 4); prediction intervals are included. Fig. 2 and 3 show that linear correlations exist between body length and calibres of the aortic and pulmonary ostia. As expected, Fig. 4 shows a linear correlation between the diameters of both ostia with the pulmonary ostium being slightly larger than the aortic ostium (1.14:1).

For a judgement of presence or absence of a narrowing of the aortic isthmus we used the index cross-sectional area of the aortic isthmus at its narrowest site divided by cross-sectional area of the descending aorta immediately distal to the ductus arteriosus or to the ligamentum arteriosum. We then defined as follows: isthmus index $<0{\cdot}81$, presence of narrowing of the aortic isthmus; isthmus index $\geq 0{\cdot}81$, absence of narrowing of the aortic isthmus. The following grouping of the material was then possible.

Group I: Isthmus index $<0{\cdot}81$ with ductus arteriosus patent, 22 cases (of which 13 were premature, 2 were immature); age after birth from 0 days up to 10 weeks;

Group II: Isthmus index $\geq 0{\cdot}81$ with ductus arteriosus patent, 9 cases (of which 8 were premature, none was immature); age after birth from 0 days up to 2 months;

Group III: Isthmus index $\geq 0{\cdot}81$ with ductus arteriosus closed, 14 cases (of which 2 were premature, none was immature); age after birth from 20 days up to 9 years.

Cases with an isthmus index $<0{\cdot}81$ together with a closed ductus arteriosus did not occur. Four observations concerning the isthmus should be mentioned: (1) narrowing of the aortic isthmus was never present in a child older than 10 weeks; (2) of the 23 prematurely born babies, which had died very young (before 11 days after birth), 13 showed a narrowing of the aortic isthmus (Table); (3) narrowing of the aortic isthmus may be severe: out of the 45 cases, 13 had an isthmus index $\leq 0{\cdot}60$, 7 an index $\leq 0{\cdot}50$ but this finding was confined to the infants less than 5 weeks old; (4) a clear correlation between isthmus index and body length was absent.

Discussion

The question dealt with in the present study has received attention over a number of decades and several approaches have been used. The sites of measuring of the ostia and arteries differ considerably in the published reports. Data on the aortic and pulmonary ostia are few, and measurements have often been made 1 to 2 cm beyond their valves (Beneke, 1878, 1879; Sinha *et al.*, 1969; Rudolph *et al.*, 1972; Bruins, 1973).

In normal cases the diameter of the annulus is as a rule smaller than the diameter of the corresponding artery beyond it, that is the ascending aorta, or pulmonary trunk (van Meurs-van Woezik and Klein, 1974). Therefore, we preferred as the sites for measurement these two ostia, the narrowest sites of the main pathways of blood flow through the heart.

In previous studies the measuring techniques have sometimes not been reported or little detail has been given (de la Cruz *et al.*, 1960; Sinha *et al.*, 1969). In addition some measurements have been made using a ruler after slitting and flattening out of the great arteries (Beneke, 1878, 1879). Different pressure on the ruler caused changes in the results of up to 4 mm (Beneke, 1878), which correspond to errors much larger than those observed using our technique, for which relatively small measuring errors have been determined (van Meurs-van Woezik and Klein, 1974). Measurement after histological sectioning has also been used (Odé, 1951), but will be inaccurate because of variable shrinkage and distortion caused by fixation, embedding, and spreading. Measurements from plastic casts (Wright, 1969; Rudolph, 1970; Rudolph *et al.*, 1972) may also not be fully reliable since we have found from personal experience that blood clots and gas bubbles may prevent correct filling by the casting material, especially at the ostia.

Clinically, echocardiography seems to be the most accurate method for measuring ostia and vessels. Our *post mortem* data for the pulmonary ostium correspond exactly with those obtained *in vivo* by Solinger *et al.* (1973) using echocardiography. However, their values for the aortic ostium are constantly 2 mm below ours, probably because measurements have not been made through the centre of this ostium, as indicated by Fig. 5 of the paper by Solinger *et al.* Other methods for clinical determination of calibres of ostia and great vessels seem inaccurate (Rodrigo and Snellen, 1953). Based on personal experience we have found that this also holds for angiographic methods as used by Sinha *et al.* (1969).

Since our study is largely concerned with growing individuals, correlation of our measurements with indices of bodily development is important. Commonly used indices of bodily development are age, body length, body weight, and body surface area. Since age is not closely related with bodily development (Tanner *et al.*, 1966) this measure, used by de la Cruz *et al.* (1960) and Eckner *et al.* (1969), is not a good choice. Furthermore in sick children body weight can change considerably within a short time. Body surface area is usually derived in part from body weight and is, therefore, also a measure of doubtful value. The most useful measure seems to be body length since it is not affected by short term changes caused by ill health. In consequence, we compared our measurements with body length. The echocardiographic data of Solinger *et al.* (1973), recalculated using the table by van Wieringen (1973) for converting body weight to body length, correspond, as mentioned, exactly to our data for the pulmonary ostium.

The data revealed linear correlations between body length and the diameters of aortic and pulmonary ostia. This is plausible because of the linear correlation between body surface, metabolism, and blood flow on the one hand and cross-sectional areas of the great vessels on the other hand.

Since the aortic isthmus with its variable calibre might act as a circulatory bottleneck and might cause clinically demonstrable differences between systolic blood pressure of the upper and lower limbs (De Swiet *et al.*, 1974), special attention has been paid to the presence and degree of narrowing (tubular hypoplasia) of the aortic isthmus in this material of normal hearts and great vessels. Our pertinent observations require some comment. In order to ascertain the presence or absence of narrowing of the aortic isthmus the question arises as to which segment of the aorta should be compared with the aortic isthmus. In our opinion this should be the descending aorta for the following reasons: before birth the total cardiac output, minus the amount of blood given off to head, neck, arms, lungs, and—in part—to the coronary arteries, reassembles in the descending aorta. After birth, when the ductus arteriosus has closed, all blood passing the aorta ostium, minus blood to head, neck, arms and—in part—to the coronary arteries, will pass via the aortic isthmus also into the descending aorta. Furthermore, since during fetal life calibres of both ascending aorta and aortic isthmus are influenced by the size of the aortic ostium, it seems less appropriate for our purpose to follow Sinha *et al.* (1969) and to compare the aortic isthmus not only with the descending aorta but also with the ascending aorta.

An internal diameter of the aortic isthmus 10 per cent less than that of the descending aorta has been chosen arbitrarily as indicative of narrowing (tubular hypoplasia). Expressed in cross-sectional areas this leads to a borderline value of 0·81 for the isthmus index (see 'subjects and method').

From our observations on normal hearts and great arteries the following conclusions on the aortic isthmus can be drawn.

(1) Under normal conditions narrowing of the aortic isthmus (isthmus index $\leq 0{\cdot}81$) may or may not exist in babies younger than 10 weeks, both in those born at term and pre- or immaturely, whereas in babies older than 10 weeks, born at term, pre-, or immaturely, narrowing of the aortic isthmus cannot be expected.

(2) In the babies younger than 5 weeks pronounced narrowing was not exceptional.

(3) No dependence of narrowing of the aortic isthmus on developmental age attained at birth seems to exist.

In conclusion it should be stressed that these observations, both those on calibres of the aortic and pulmonary ostia and those on the aortic isthmus, characterise quantitative aspects of the normal vasculature. The definition of borderline values between normal and pathological conditions is a desirable next step which we have not yet attempted. However, the data reported provide a necessary starting point for defining such borderline values.

References

Beneke, F. W. (1878). *Die anatomischen Grundlagen der Constitutionsanomalieen des Menschen.* N. G. Elwert, Marburg (Germany).

Beneke, F. W. (1879). *Ueber das Volumen des Herzens und die Weite der Arteria pulmonalis und Aorta ascendens in den verschiedenen Lebensaltern.* Theodor Kay, Cassel (Germany).

Bruins, C. L. D. Ch. (1973). De arteriële pool van het hart: wisselwerking tussen bloedstroom en hart-vaatstelsel, getoetst aan enkele aangeboren hartvaatgebreken. Thesis, Leiden (The Netherlands).

de la Cruz, M. V., Anselmi, G., Romero, A., and Monroy, G. (1960). A qualitative and quantitative study of the ventricles and great vessels of normal children. *American Heart Journal,* **60,** 675–690.

de Swiet, M., Peto, J., and Shinebourne, E. A. (1974). Difference between upper and lower limb blood pressure in normal neonates using Doppler technique. *Archives of Disease in Childhood,* **49,** 734–735.

Eckner, F. A. O., Brown, B. W., Davidson, D. L., and Glagov, S. (1969). Dimensions of normal human hearts. *Archives of Pathology,* **88,** 497–507.

Gorlin, R., and Gorlin, S. G. (1951). Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves and central circulatory shunts. *American Heart Journal,* **41,** 1–29.

Kloosterman, G. J. (1973). *De voortplanting van de mens.* Centen, Bussum (The Netherlands).

Krediet, P. (1962). Anomalies of the arterial trunks in the thorax and their relation to normal development. Thesis, Utrecht (The Netherlands).

Krediet, P. (1963). Isthmus stenosis and coarctation. In *Second European Anatomical Meeting,* p. 88–89. International Congress Series No. 70. Excerpta Medica, Amsterdam.

Krediet, P. (1965). A hypothesis of the development of coarctation in man. *Acta Morphologica Neerlando-Scandinavica,* **6,** 207–212.

May, N. D. S. (1968). Experimental studies of the collateral circulation in the head and neck of sheep *(Ovis aries). Journal of Anatomy,* **103,** 171–181.

Odé, E. (1951). De ductus arteriosus. Thesis, Leiden (The Netherlands).

Rodrigo, F. A., and Snellen, H. A. (1953). Estimation of valve area and 'valvular resistance'. A critical study of the physical basis of the method employed. *American Heart Journal,* **45,** 1–12.

Rudolph, A. M. (1970). The changes in the circulation after birth. Their importance in congenital heart disease. *Circulation,* **41,** 343–359.

Rudolph, A. M., Heymann, M. A., and Spitznas, U. (1972). Hemodynamic considerations in the development of narrowing of the aorta. *American Journal of Cardiology,* **30,** 514–525.

Sachs, L. (1973). *Angewandte Statistik.* Springer, Berlin, Heidelberg, and New York.

Sinha, S. N., Kardatzke, M. L., Cole, R. B., Muster, A. J., Wessel, H. U., and Paul, M. H. (1969). Coarctation of the aorta in infancy. *Circulation,* **40,** 385–398.

Solinger, R., Elbl, F., and Minhas, K. (1973). Echocardiography in the normal neonate. *Circulation,* **47,** 108–118.

Tanner, J. M., Whitehouse, R. H., and Takaishi, M. (1966). Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. *Archives of Disease in Childhood,* **41,** 454–471; 613–635.

van Meurs-van Woezik, H., and Klein, H. W. (1974). Calibres of aorta and pulmonary artery in hypoplastic left and right heart syndromes: effects of abnormal bloodflow? *Virchows Archiv Abteilung A. Pathological Anatomy and Histology,* **364,** 357–364.

van Wieringen, J. C. (1973). Lengte en gewicht van kinderen. *Maandschrift voor Kindergeneeskunde,* **41,** 69–80.

Wright, N. L. (1969). Dissection study and mensuration of the human aortic arch. *Journal of Anatomy,* **104,** 377–385.

Yang, S. S., Bentivoglio, L. G., Maranhão, V., and Goldberg, H. (1972). *From Cardiac Catheterization Data to Hemodynamic Parameters.* F. A. Davis, Philadelphia.

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Hypertensive pulmonary vascular disease in children
Detection by radioactive nitrogen (^{13}N) inhalation and injection

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Regional lung function has been studied in 16 children with intracardiac shunts and a variety of associated cardiac anomalies using radioactive nitrogen (^{13}N) and a gamma camera-computer system. The distribution and washout of inhaled ^{13}N were usually normal. The distribution of intravenously injected ^{13}N was often abnormal and could be related to local anatomy. The most important finding was delayed clearance by ventilation of intravenously injected ^{13}N in children with an abnormally raised pulmonary/systemic vascular resistance ratio (Rp/Rs) at cardiac catheterisation. The regional localisation of this ventilation-perfusion imbalance could be related in several children to the probable distribution of hypertensive pulmonary vascular disease, predicted either from local anatomy shown at cardiac catheterisation or from the abnormal distribution of pulmonary perfusion. Abnormalities present on breathing air may be partially reversed on breathing 100 per cent oxygen.

Hypertensive pulmonary vascular disease in children with congenital cardiac defects greatly influences operative risks (Cartmill *et al.*, 1966; Espino-Vela *et al.*, 1968), postoperative course (Park *et al.*, 1969), and long-term haemodynamic results (Braunwald *et al.*, 1962; Maron *et al.*, 1973; Allen *et al* 1974; Whitman and Ellis, 1975). Hypertensive pulmonary vascular disease is generally considered to be present when the pulmonary vascular resistance or the pulmonary: systemic resistance ratio (Rp/Rs) calculated at cardiac catheterisation is abnormally raised (Braunwald *et al.*, 1962; Kirklin, 1965; Allen *et al.*, 1974).

We have recently developed a free breathing technique for studying regional lung function in children of all ages using radioactive nitrogen (^{13}N) and a gamma camera (Godfrey *et al*, 1975; Ronchetti *et al.*, 1975) and have found a consistent pattern of abnormality in children with hypertensive pulmonary vascular disease. We present our observations on this phenomenon which could provide a simpler method for the detection and evaluation of pulmonary vascular disease.

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Subjects and methods

Sixteen children aged 7 months to 12 years were studied. Each had been referred for investigation of congenital heart disease and had undergone cardiac catheterisation. The anatomical diagnoses and cardiac catheterisation results are shown in Table 1. The pulmonary: systemic resistance ratio (Rp/Rs) was calculated by the standard technique (Grossman, 1974) using the pulmonary arteriolar resistance in the numerator. Pulmonary and systemic flows were derived by the Fick principle. Taking the upper normal limit for Rp/Rs as 0·25 (Kirklin 1965), cases 1 to 4 were considered not to have hypertensive pulmonary vascular disease. Most of the remaining patients had a raised Rp/Rs ratio indicative of hypertensive pulmonary vascular disease. Cases 15 and 16 had complex anatomy with a large systemic-pulmonary anastomosis supplying only part of the pulmonary vascular bed, precluding calculation of Rp/Rs, while case 7 had multiple peripheral pulmonary stenoses with a normal mean pulmonary arterial pressure distal to the stenosis in the right lower lobe. In cases 10 and 11, Rp/Rs fell after inhalation of 100 per cent oxygen.

Regional lung function studies were performed as previously described (Ronchetti *et al.*, 1975), with the child lying supine over the gamma camera and breathing air spontaneously. Cases 6 and 10 were also studied while breathing 100 per cent oxygen. The younger children were lightly sedated with diazepam. ^{13}N was made by the Medical Research Council Cyclotron Unit and piped directly to the adjacent room for immediate use because of its short half-life (10 minutes). For the study of ventilation, a 4 ml bolus of the gas was delivered at end-expiration into the nasopharynx via an infant feeding tube or through a mouthpiece. For the study of pulmonary perfusion, a bolus of ^{13}N was dissolved in 4 ml isotopic saline and was injected rapidly via an indwelling needle into an arm vein. Because of the extreme insolubility of ^{13}N, virtually all the injected isotope reaching the pulmonary capillaries passed rapidly into alveoli and was then washed out by ventilation. During and after each administration of isotope the lungs were scanned continuously by a gamma camera for 5 to 10 minutes and the data stored on magnetic tape. Data processing was performed with the aid of a digital computer. For each study, an image of the counts over the lungs was displayed on an oscilloscope and each lung field was divided into an upper and lower zone using a light pen. Correction was made for camera uniformity, for background activity which included activity reaching the systemic circulation by right-to-left shunting, and for isotope decay. Activity time curves were plotted for each lung zone and indices of regional lung function calculated as described below.

Calculation of results

A distribution index (DI) for each zone for both ventilation and perfusion was calculated from the following equation:

$$DI = \frac{\text{Regional counts}}{\text{Whole lung counts}} \div \frac{\text{Regional area}}{\text{Whole lung area}}$$

Assuming that relative regional image areas reflect regional volumes, even distribution of ventilation or perfusion throughout the lungs would be denoted in each zone by a distribution index of 1·0 (Ronchetti *et al.*, 1975). This assumption is not always valid in children with cardiac disease since an enlarged heart may distort pulmonary anatomy. However, it is possible to derive an improved regional 'volume-corrected' perfusion distribution index in children with uniform regional ventilation. Since ventilation is then directly proportional to lung volume, the perfusion distribution index for each zone of the lung is the distribution index for that zone in the perfusion study, divided by the equivalent distribution index in the ventilation study. It is necessary for this index that the areas on the oscilloscope image for both studies should be identical.

For a better analysis of the washout curves independent of assumption about lung volumes, a transfer function (H/A) has been calculated by dividing the peak height (H) of the curve by the area (A) under the washout portion (Ronchetti *et al.*, 1975). In the inhalation study, H/A represents ventilation per unit lung volume (fractional ventilation) but in the study with injected ^{13}N it is a complex function of ventilation, perfusion, and lung volume (Winlove *et al.*, 1976). The washout curves from both studies would be identical if alveolar ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) were evenly matched. Any difference between the curves is, therefore, an index of ventilation/perfusion ($\dot{V}/\dot{Q}$) imbalance resulting from reduced $\dot{V}/\dot{Q}$ ratios (Fig 1). A normal range of H/A values has been obtained from studies of 20 normal lung zones in 10 children with localised lung disease (Winlove *et al.*, 1976). For ventilation, the mean H/A is 3·65 with a range (±2 SD on a logarithmic scale) 2·23–6·08 and for perfusion it is 2·82 with a similar range 2·08–4·39. We have, therefore, taken 2·0 as the lower normal limit for H/A in both studies.

Table 1 *Patients studied, diagnoses, and Rp/Rs values*

Case No.	*Age (y)*	*Diagnosis*	*Rp/Rs*
1	4	VSD; peripheral pulmonary stenoses	0·06
2	6	Tetralogy of Fallot	0·09
3	4	VSD	0·10
4	2	VSD	0·22
5	14/12	VSD	0·32
6	3	VSD	0·45
7	3	VSD; peripheral pulmonary stenoses to all regions except right upper zone	0·54†
8	8	Total anomalous pulmonary venous drainage	0·61
9	6	VSD	0·63
10	7/12	Secundum ASD and VSD	0·75 0·20*
11	5	VSD	0·76 0·17*
12	15/12	Persistent ductus arteriosus	0·89
13	4	VSD	1·66
14	3	Primary pulmonary hypertension	2·55
15	3	Tetralogy of Fallot, Waterston shunt	Not calculable
16	12	Pulmonary atresia, Blalock-Taussig shunt; absent right pulmonary artery	Not calculable

*While breathing 100 per cent oxygen.

†Calculated using pulmonary arterial pressure proximal to the stenoses.

VSD, ventricular septal defect; ASD, atrial septal defect; Rp/Rs, pulmonary/systemic resistance ratio.

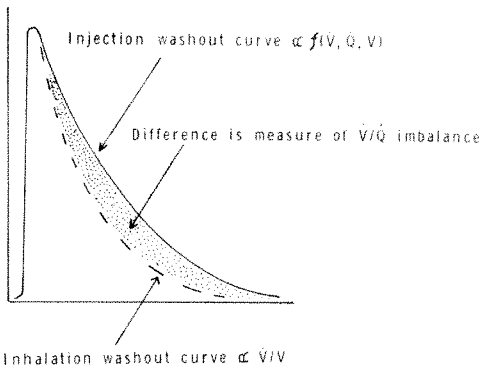
Injection washout curve ∝ ƒ(V̇, Q̇, V)
Difference is measure of V̇/Q̇ imbalance
Inhalation washout curve ∝ V̇/V

Fig. 1 *Schematic curves for washout of ^{13}N after injection and inhalation. $\dot{V}$, ventilation; $\dot{Q}$, perfusion; V, volume.*

Results

VENTILATION

As shown in Table 2, the fractional ventilation of inhaled ^{13}N was abnormal only in one zone of one child (case 4) and showed regional variation in one further child (case 15). Both children had previously undergone intrathoracic surgery. Fractional ventilation was not calculable for case 10 as data from the bolus inhalation were not available.

PERFUSION

Abnormalities of the washout (H/A) after injection. of ^{13}N were present in several children and could be related both to the elevation of Rp/Rs and to regional anatomy. On the basis of these results, the children were divided into groups:

Group 1 (cases 1 to 4)
All values of H/A after injection and Rp/Rs were normal. Fig 2 shows the washout curves after both inhalation and injection of ^{13}N in case 3 and is typical of the group.

Group 2 (cases 5, 9, 10, 12, 13, 14, and 16)
In this group washout after injection was abnormally slow in at least 3 lung zones. Haemodynamic evidence for hypertensive pulmonary vascular disease was present in each patient except case 16, in whom calculation of Rp/Rs was not possible. The washout curves of case 12 are shown in Fig 3. In case 10 the changes were partially reversed while breathing 100 per cent oxygen.

Group 3 (cases 6, 7, 8, 11, and 15)
Local abnormalities of washout after injection were present in these patients and all had haemodynamic evidence of hypertensive pulmonary vascular disease. In cases 8 and 11 in whom the pulmonary vascular disease was thought to be early and reversible the abnormalities occurred in the regions of

Table 2 *Results of regional lung function studies*

Case No.	*Perfusion distribution index (PDI)*				*Fractional ventilation (H/A)*				*Washout after infusion (H/A)*			
	RU	*RL*	*LU*	*LL*	*RU*	*RL*	*LU*	*LL*	*RU*	*RL*	*LU*	*LL*
1	0·91	0·66	2·59	1·86	2·69	2·89	2·94	2·69	2·09	2·17	2·15	2·14
2	1·67	1·32	0·31	0·69	2·40	2·31	2·49	1·98	5·93	3·04	4·28	2·48
3	1·06	1·09	0·79	1·35	3·72	3·47	4·12	3·69	2·52	3·33	3·82	3·49
4	*	*	*	*	1·88	2·09	3·05	3·72	2·71	2·46	3·02	2·27
5	1·02	0·84	0·87	2·19	3·61	3·66	4·46	2·85	1·75	1·98	2·33	1·01
6	1·09	0·78	1·72	0·76	5·02	4·90	3·28	3·99	2·55	2·56	1·66	1·09
									2·67	3·22	2·03	1·34†
7	0·98	1·09	1·08	0·78	3·21	2·68	2·42	2·44	1·28	2·01	2·13	2·18
8	0·72	0·69	1·46	1·40	3·80	3·27	3·39	3·79	2·60	4·27	1·23	1·75
9	1·28	0·92	1·01	0·73	3·86	3·54	4·29	3·91	2·27	1·63	1·63	1·29
10	1·19	1·10	1·03	0·94	Not calculable				0·86	1·33	0·66	0·91
									1·28	2·44	1·14	1·65†
11	0·67	1·22	0·81	1·65	4·03	3·48	4·05	3·71	5·97	4·33	4·72	2·12
12	0·85	1·13	1·36	1·44	1·44	3·28	3·19	2·58	0·87	0·74	1·45	1·40
13	1·11	0·81	1·35	0·93	2·27	2·66	2·20	2·47	0·98	1·06	1·21	0·79
14	0·43	0·31	1·95	1·833	4·28	4·29	3·48	4·22	0·94			1·75
15	*	*	*	*	2·11	2·40	3·90	4·33	3·36	1·95	3·95	3·36
16	1·43	0·74	1·33	1·03	3·20	2·61	3·38	3·15	2·84	1·56	1·41	0·69

*Perfusion distribution index not calculable because of regional variation in fractional ventilation.
†While breathing 100 per cent oxygen.
RU, right upper zone; LU, left upper zone; RL, right lower zone; LL, left lower zone.

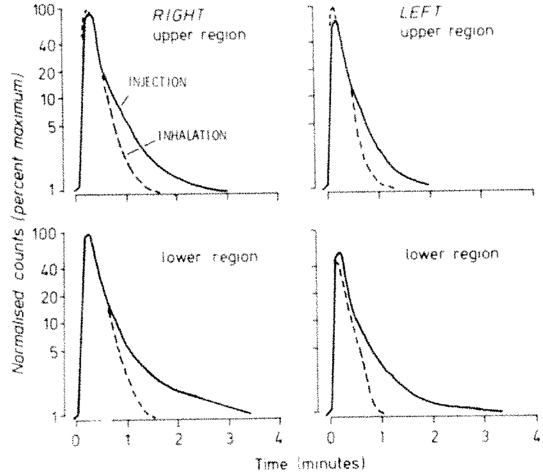

Fig. 2 *Washout curves for case 3 showing rapid washout of* ^{13}N *after both injection and inhalation.*

greatest perfusion. Two patients had unusual anatomy and their abnormalities were restricted to areas either where there was no protective pulmonary stenosis (case 7) or where there was a large systemic-pulmonary shunt (case 15). In case 6 there was overall improvement in the washout curves after injection while breathing 100 per cent oxygen but washout in the left lower zone was still abnormally slow. Fig 4a shows the localised delay in washout in case 7 and Fig 4b is the pulmonary angiogram of the same patient showing stenoses of the left main pulmonary artery and the inferior branch of the right pulmonary artery.

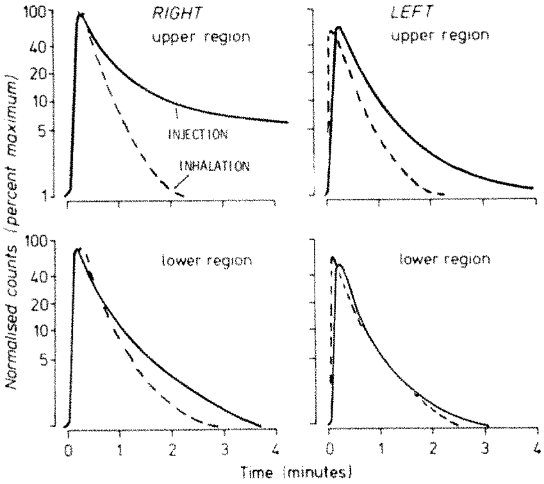

Fig. 4a *Washout curves for case 7 showing a localised delay in washout of* ^{13}N *after injection.*

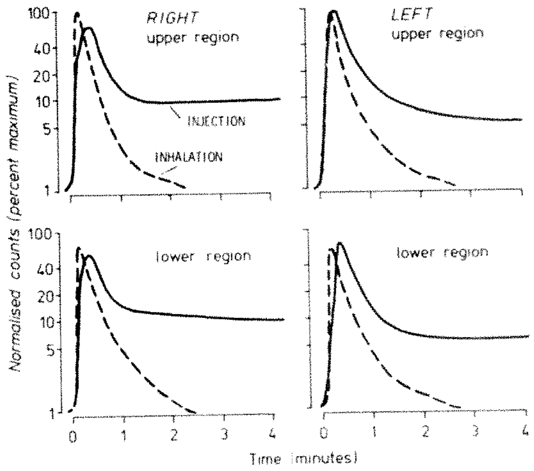

Fig. 3 *Washout curves for case 12 showing generalised delay in washout of* ^{13}N *after injection.*

Discussion

There appears to be a consistent pattern of abnormality in ^{13}N washout after intravenous injection in children with hypertensive pulmonary vascular disease. All patients in group 2, with the exception of case 16, had normal pulmonary artery anatomy and haemodynamic evidence of hypertensive pulmonary vascular disease. All had generalised delay

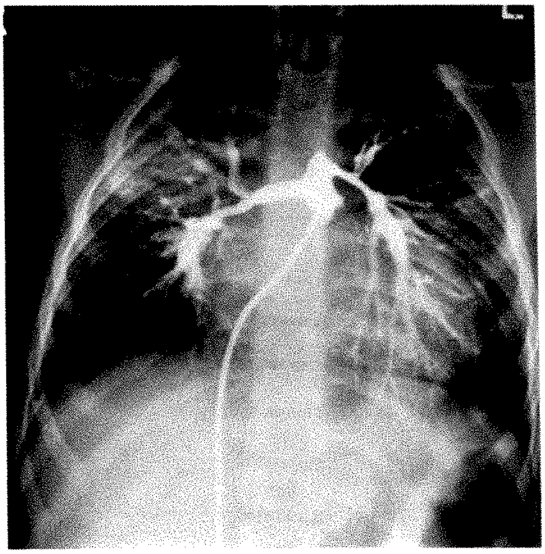

Fig. 4b *Pulmonary angiogram of case 7 showing hypoperfusion of the left lung and lower zone of the right lung.*

in washout after injection of ^{13}N. In contrast, those patients in group 3 with abnormal pulmonary artery anatomy had related localised abnormalities in washout. Though Rp/Rs could not be calculated in case 16, he would appear from this study to have hypertensive pulmonary vascular disease affecting mainly the left lung, the side of the Blalock-Taussig shunt. The flow to this lung was relatively low, indicating that the hypertensive pulmonary vascular disease was severe and flow-limiting. In this context it is interesting that Alderson *et al.* (1976) found diminished pulmonary perfusion on the side of the shunt in patients with previous shunt operations for tetralogy of Fallot. Their demonstration of relatively normal regional ventilation using ^{133}Xe scans is confirmed in this study and is shown to be true even in the presence of severe hypertensive pulmonary vascular disease.

The delay in clearance of ^{13}N in the injection study indicates that a proportion of the gas is entering perfused but extremely poorly ventilated alveoli. Such a $\dot{V}/\dot{Q}$ imbalance should produce systemic arterial desaturation, and this has been noted previously in patients with primary pulmonary hypertension (Wood, 1952). Several authors have investigated the causes of the increased alveolar-arterial oxygen gradient ((A–a) DO_2) in both children (Lees *et al.* (1967) and adults (Woolf, 1963; Wessel *et al.*, 1964) with intracardiac shunts or primary pulmonary hypertension. Studies in dogs with pulmonary hypertension caused either by surgically produced systemic-pulmonary anastomosis (Ellison *et al.*, 1961) or the heart-worm *Dirofilaria immitis* (Kentera *et al.*, 1965) have confirmed an increased (A–a) DO_2 whose severity is related to the pulmonary artery pressure. Several of these authors (Ellison *et al.*, 1961; Kentera *et al.*, 1965; Lees *et al.*, 1967) have concluded from the effects on (A–a) DO_2 of high inspired oxygen concentrations that venous admixture through pulmonary arteriovenous shunts rather than $\dot{V}\dot{Q}$ imbalance is the primary cause of the arterial desaturation. It is not possible to interpret our results in this manner, however, since venous admixture of this type would produce rapid removal of isotope into the systemic circulation with effective elimination from the record with background correction. The efficacy of this correction can be seen from the results of case 2 who had Fallot's tetralogy with a large right-to-left shunt and yet normal perfusion washout curves (Table 2). Our results can only be interpreted in terms of $\dot{V}/\dot{Q}$ imbalance; a proportion of the injected ^{13}N enters regions of alveoli which are so poorly ventilated that they do not contribute significantly to the fractional ventilation measured after inhalation of ^{13}N which, therefore, remains normal. These regions would probably not become completely oxygenated when breathing 100 per cent oxygen and hence would not have been considered as $\dot{V}/\dot{Q}$ imbalance in the previous studies (Ellison *et al.*, 1961; Kentera *et al.*, 1965; Lees *et al.*, 1967).

The physiological mechanisms underlying these observations remain a mystery so far but one tentative explanation might be a 'closing volume' type of effect whereby a substantial proportion of small airways are occluded for part of the respiratory cycle. This is known to occur, for example, when there is loss of elastic recoil as in emphysema. The alveoli supplied by such airways would receive intravenous ^{13}N but not inhaled ^{13}N and would cause the difference in the shape of the respective washout curves. The pathological mechanism responsible for such a phenomenon, or indeed for any other mechanism causing our observed $\dot{V}/\dot{Q}$ imbalance, is unknown. We know of no histological evidence for small airway obstruction and it is unlikely to be caused by oedema as this is not a feature of chronic pulmonary hypertension (Damman and Ferencz, 1956). Gradual improvement of (A–a) DO_2 in association with gradual reduction in pulmonary artery pressure has been shown in one dog after ligation of a systemic-pulmonary anastomosis (Ellison *et al.*, 1961). We have shown some acute improvement in ^{13}N washout after injection in cases 6 and 10 while breathing 100 per cent oxygen. In case 10, Rp/Rs was also reduced at cardiac catheterisation in response to 100 per cent oxygen but the implications of this and of other current attempts to determine closing volumes are as yet uncertain. It appears, therefore, that the $\dot{V}/\dot{Q}$ imbalance in this study can be associated with reversible pulmonary vascular disease.

Regional lung function studies using ^{13}N are easy to perform on children of all ages. The radiation dose (200–400 m.rads) is only a fraction of that received at cardiac catheterisation. There is, furthermore, the advantage over catheterisation that regional information is obtained which may be of value in detecting localised early hypertensive pulmonary vascular disease. Unfortunately, because of the short half-life of the isotope, studies must be performed in the close vicinity of a cyclotron. We are currently exploring the use of the more widely available isotope ^{133}Xe which has a much longer half-life but is more soluble than ^{13}N. It is probable that it will be possible to use ^{133}Xe but care will be needed to ensure that only a small dose is used if delayed clearance is anticipated because of this long half-life and slow biological clearance. The sensitivity and specificity of the technique are as yet uncertain but our preliminary results are encouraging. These studies may be particularly valuable for repeated assessment of children with complicated cardiac defects in whom early hypertensive pulmonary vascular disease is a common complication, in order to determine the optimum time for corrective surgery.

We wish to thank our colleagues from the MRC Cyclotron Unit and the Department of Medical Physics for their wholehearted support which makes these investigations in sick children possible.

References

Alderson, P. O., Boonvisut, S., McKnight, R. C., and Hartman, A. F. (1976). Pulmonary perfusion abnormalities and ventilation-perfusion imbalance in children after total repair of tetralogy of Fallot. *Circulation,* **53,** 332–337.

Allen, H. D., Anderson, R. C., Noren, G. R., and Moller, J. H. (1974). Postoperative follow-up of patients with ventricular septal defect. *Circulation,* **50,** 465–471.

Braunwald, N. S., Braunwald, E., and Morrow, A. G. (1962). The effects of surgical abolition of left to right shunts on the pulmonary vascular dynamics of patients with pulmonary hypertension. *Circulation,* **26,** 1270–1278.

Cartmill, T. B., DuShane, J. W., McGoon, D. C., and Kirklin, J. W. (1966). Results of repair of ventricular septal defect. *Journal of Thoracic and Cardiovascular Surgery,* **52,** 486–499.

Damman, J. F., and Ferencz, C. (1956). The significance of the pulmonary vascular bed in congenital heart disease. *American Heart Journal,* **52,** 210–231.

Ellison, L. T., Hall, D. P., Yeh, T., Mobarhan, H., Rossi, J., and Ellison, R. G. (1961). Physiological alterations in increased pulmonary blood flow with and without pulmonary hypertension. *Journal of Applied Physiology,* **16,** 305–308.

Espino-Vela, J., Cardenas, N., and Cruz, R. (1968). Patent ductus arteriosus. With special reference to patients with pulmonary hypertension. *Circulation,* **37-38,** Suppl. V, V-45–60.

Godfrey, S., Ronchetti, R., Stocks, J., and Hallidie-Smith, K. (1975). Generalised pulmonary hyperinflation and Fallot's Tetralogy in a neonate investigated by pulmonary physiological and radioisotopic methods. *Thorax,* **30,** 452–460.

Grossman, W. (1974). *Cardiac Catheterization and Angiography.* Lea and Febiger, Philadelphia.

Kentera, D., Wallace, C. R., Hamilton, W. F., and Ellison, L. T. (1965). Venous admixture in dogs with chronic pulmonary hypertension. *Journal of Applied Physiology,* **20,** 919–921.

Kirklin, J. W. (1965). Ventricular septal defect with pulmonary vascular disease. *New Zealand Medical Journal* (Cardiac Suppl.), **64,** 34–36.

Lees, M. H., Way, R. C., and Ross, B. B. (1967). Ventilation and respiratory gas transfer of infants with increased pulmonary blood flow. *Pediatrics,* **40,** 259–271.

Maron, B. J., Redwood, D. R., Hirshfeld, J. W., Goldstein, R. E., Morrow, A. G., and Epstein, S. E. (1973). Postoperative assessment of patients with ventricular septal defect and pulmonary hypertension. Response to intense upright exercise. *Circulation,* **48,** 865–874.

Park, C. D., Nicodemus, H., Downes, J. J., Miller, W. W., and Waldhausen, J. A. (1969). Changes in pulmonary vascular resistance following closure of ventricular septal defects. *Circulation,* **39-40,** Suppl. I, I-193–200.

Ronchetti, R., Stocks, J., Freedman, N., Glass, H., and Godfrey, S. (1975). Clinical application of regional lung function studies in infants and small children using ^{13}N. *Archives of Disease in Childhood,* **50,** 595–603.

Wessel, H. U., Kezdi, P., and Cugell, D. W. (1964). Respiratory and cardiovascular function in patients with severe pulmonary hypertension. *Circulation,* **29,** 825–832.

Whitman, V., and Ellis, N. G. (1975). Pulmonary hemodynamics after repair of left to right shunt lesions associated with pulmonary artery hypertension. *Progress in Cardiovascular Diseases,* **17,** 467–473.

Winlove, P., Freedman, N., Fitzpatrick, M. L., and Godfrey S. (1976). The quantitation of regional lung function in infants and children using radioactive nitrogen (^{13}N). *(Submitted.)*

Wood, P. (1952). Pulmonary hypertension. *British Medical Bulletin,* **8,** 348–353.

Woolf, C. R. (1963). Pulmonary function in adults with intracardiac septal defect. *Circulation,* **27,** 261–267.

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Multifocal atrial tachycardia in two neonates

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Two neonates with rapid and irregular pulse rate had an uncommon form of atrial tachycardia. The irregular heart rate was first detected during fetal monitoring. Postnatal electrocardiograms were compatible with the diagnosis of multifocal atrial tachycardia or chaotic atrial rhythm. Both patients were treated with digoxin and the rhythm gradually reverted to sinus. This may represent the first description of multifocal atrial tachycardia in the newborn.

Multifocal atrial tachycardia is an uncommon form of atrial arrhythmia which results in irregularly irregular pulse. This unusual form of supraventricular tachycardia is usually seen in elderly patients with lung disease. To the best of our knowledge, multifocal atrial tachycardia has not been reported in neonates. This report describes two asymptomatic neonates who presented with rapid and irregularly irregular heart rate and who were found to have multifocal atrial tachycardia.

Case reports

CASE 1

A 4-day-old full-term male infant was transferred to Children's Hospital of Michigan because of rapid and irregular heart rate. The pregnancy was uneventful. The mother had been treated with three grains of dessicated thyroid daily during pregnancy and for 19 years previously. Labour was induced because of irregular fetal heart tones, with an average rate of 100 per minute. Apart from the irregular heart rhythm, the physical examination was normal. There was no evidence of congestive heart failure. The chest *x*-ray film showed normal heart size, normal vascularity, and left aortic arch. The electrocardiogram disclosed right axis deviation, an rsR′ pattern in V3R and V1 and chaotic atrioventricular rhythm. Fig. 1 (A and B) shows selected strips of lead V1. The average atrial rate was 250 per minute, and the ventricular rate ranged between 150 and 250 per minute. The PP, RR, and PR intervals were variable. There were 5 different types of P waves present (a, b, c, d, and e), with a distinct isoelectric baseline between them. The arrow in Fig. 1 B shows a nonconducted atrial premature depolarisation and aberrantly depolarised ventricular complexes.

The patient was given oral digoxin, which produced gradual slowing of the ventricular rate and decreasing atrial ectopy. The electrocardiogram on the third day of treatment (Fig. 1 C) showed three types of P waves (a, b, d), the atrial rate ranged between 150 and 250 per minute, the ventricular rate ranged between 90 and 180 per minute, and there was an occasional ventricular complex with aberrant conduction. The laboratory data including microprotein-bound iodine were normal. One week after digitalis the electrocardiogram showed sinus rhythm with right bundle-branch block pattern. At 1 year of age digitalis was stopped, and no arrhythmias occurred during the subsequent 2 years of follow-up.

CASE 2

A 24-hour-old full-term male infant was referred to Children's Hospital of Michigan because of an irregular and rapid heart rate. The pregnancy was uncomplicated. Labour had been induced because of irregular fetal heart sounds. The physical examination was normal except for an irregularly irregular heart rate ranging between 120 and 150 per minute. There was no congestive heart failure. The chest *x*-ray film disclosed normal heart size, normal vascularity, and left aortic arch. The electrocardiogram showed right axis deviation with no evidence of chamber enlargement. Fig. 2 shows the selected strips of lead II; Fig. 2 A and B were obtained on admission, when the atrial rate was rapid and irregular (range: 115 to 500 per minute). The ventricular rate was irregular and rapid (range: 115 to 200 per minute). The PP, RR, and PR intervals were variable with 3 different types of P waves

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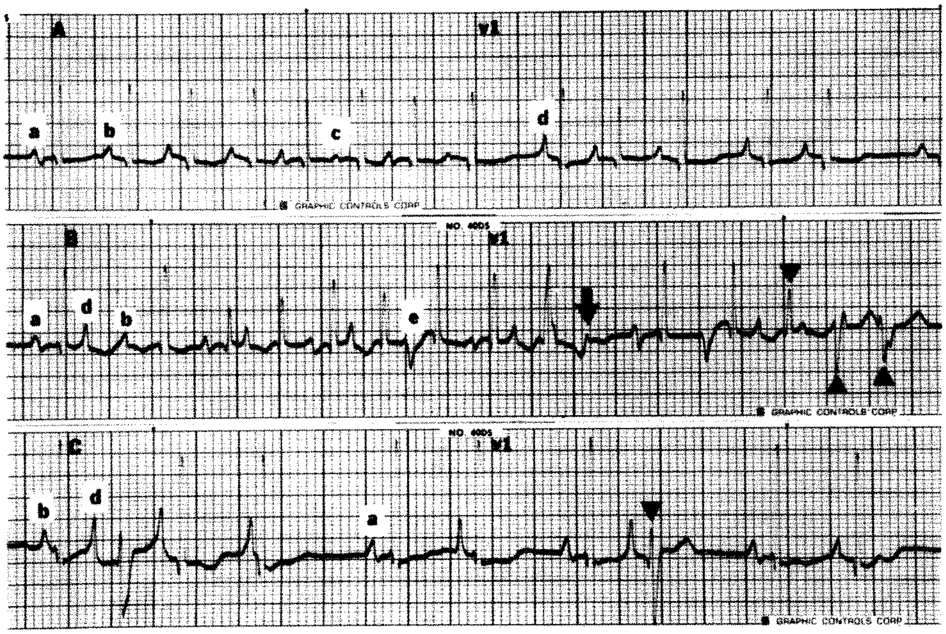

Fig. 1 *Electrocardiogram recorded at 50 mm/s. (A) and (B) are the strips of lead V1 recorded on admission. The PP, PR, and RR intervals are variable, and 5 types of P waves (a, b, c, d, e) are present. The arrow points toward nonconducted atrial premature depolarisation. The triangles point toward aberrantly conducted ventricular complexes. (C) A strip of lead V1 recorded at double sensitivity (1 mV=20mm) after digitalis. There are 3 types of P waves (a, b, d) present. The ventricular rate has decreased.*

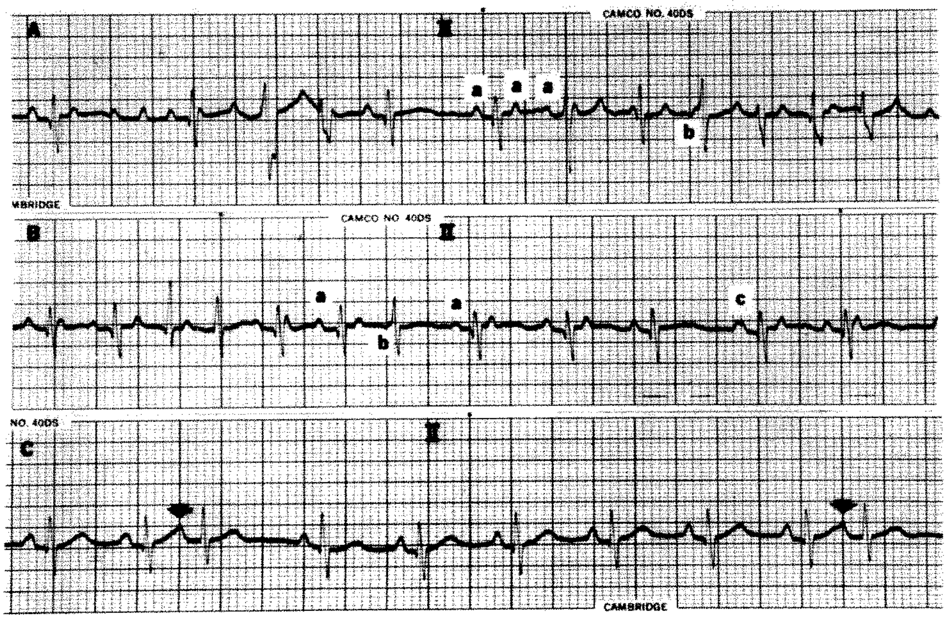

Fig. 2 *Electrocardiogram recorded at 50 mm per second. (A) and (B) Strips of lead V1 recorded on admission. PP, PR, and RR intervals are variable, and 3 types of P wave (a, b, c) are present. (C) Strip of lead V1 recorded after digitalisation. There are unifocal atrial premature beats (arrows) present.*

(a, b, c). There was a distinct isoelectric interval present between the d waves. There were ventricular complexes with aberrant conduction.

The baby was treated with oral digoxin and the ectopic atrial activity was significantly depressed by the fourth day. The electrocardiogram after 1 week of digoxin therapy (Fig. 2 C) showed sinus rhythm with uniforcal atrial premature beats (arrows). By the end of the second week of treatment, the atrial premature beats had disappeared. During the follow-up period of approximately 5 months the rhythm remained sinus. At present the baby is on digoxin and is asymptomatic.

Comments

Both babies had irregular heart rates prenatally and this was mistaken for fetal distress. There were no associated heart defect or congestive heart failure. The pulse was rapid and irregularly irregular and the electrocardiogram in both cases was characterised by: fast atrial rate, chaotic atrial rhythm with P waves of more than 3 different configurations, the presence of an isoelectric baseline between the P waves, and a variable degree of atrioventricular block. These electrocardiographic features fulfil the criteria for the diagnosis of multifocal atrial tachycardia or chaotic atrial rhythm. The published reports (Shine *et al.*, 1968; Chung, 1971; Berlinerblau and Feder, 1972) indicate that multifocal atrial tachycardia is usually seen in elderly patients with bronchopulmonary disease and digitalis intoxication. We were unable to find any reports concerning chaotic atrial rhythm in neonates. It is interesting to point out that the response to digoxin in our cases was complete but slow. Initially there was slowing of the atrioventricular conduction which resulted in decreased ventricular rate. This was followed by a gradual decrease in atrial ectopic activity and sinus rhythm was well established by the end of the second week of digoxin therapy. Once the sinus rhythm had been established, recurrence of ectopic atrial activity did not occur during the follow-up period extending up to 3 years.

References

Berlinerblau, R., and Feder, W. (1972). Chaotic atrial rhythm. *Journal of Electrocardiology*, **5**, 135-144.

Chung, E. K. (1971). Appraisal of multifocal atrial tachycardia. *British Heart Journal*, **33**, 500-504.

Shine, K. I., Kastor, J. A., and Yurchak, P. M. (1968). Multifocal atrial tachycardia—Clinical and electrocardiographic features in 32 patients. *New England Journal of Medicine*, **279**, 344-349.

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Coronary artery disease and its risk factors in families of young men with angina pectoris and in controls

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The occurrence of coronary artery disease and its risk factors were assessed in 560 relatives of 104 men who developed angina pectoris before the age of 56 and in 498 relatives of 94 controls in two geographical areas, one with a moderate (South Finland) and another with a high (East Finland) incidence of coronary artery disease.

The risk of dying from coronary artery disease before the age of 65 was 5 times greater for fathers of patients (25%) than for fathers of controls. For brothers of patients, the risk of developing fatal or non-fatal coronary artery disease was about 60 per cent which is 5·5 times greater than that for brothers of controls. The corresponding risk for sisters of patients was 30 per cent, which is 2·5 times greater than that for sisters of controls. The risk was not increased for mothers of patients. One quarter of families of patients showed distinct clustering of coronary artery disease (3 or more cases of coronary artery disease before the age of 65). Hyperlipidaemla, hypertension, and diabetes were 2 to 6 times more common among sibs free of clinical coronary artery disease in the families of patients compared with sibs in the families of controls.

Coronary artery disease, hyperlipidaemia, and hypertension were significantly more common in control families in the East than in the South; the difference between families of patients in the two areas was less pronounced. Increased rate of coronary artery disease is closely associated with the increased prevalence of hyperlipidaemia and hypertension in families of patients in both areas and in control families in the East.

Familial occurrence of coronary artery disease has been well documented in both family (Shanoff *et al.*, 1961; Rose, 1964; Slack and Evans, 1966) and twin (Harvald and Hauge, 1970; Liljefors, 1970; de Faire, 1974) studies. The first-degree relatives of coronary patients are reported to have a 2·5- to 7-fold increase in the risk of coronary death (Slack and Evans, 1966). The familial nature of coronary artery disease may be explained partly by the common environmental factors shared by the family members and partly by the known genetic component of individual risk factors associated with coronary artery disease. Thus, hyperlipidaemia, a potent precursor of coronary artery disease, has recently been shown in a large proportion of relatives of young patients with myocardial infarction (Goldstein *et al.*, 1973; Nikkilä and Aro, 1973) and hereditary factors are involved also in hypertension (Miall, 1971) and diabetes (Tattersall and Fajans, 1975). However, no analysis has thus far been made of the occurrence of all these risk factors in the families of patients with manifest coronary artery disease. It is, therefore, not known to what extent hyperlipidaemia, hypertension, and diabetes cluster into the families of coronary patients and how much of the familial component of coronary artery disease is accounted for by these known risk factors.

Finland is a country with a unique genetic pattern of multiple rare genes (Nevanlinna, 1972) and with the world's highest prevalence and mortality of coronary artery disease in middle-aged men (Epstein and Krueger, 1969). Moreover, distinct regional differences in the rate of coronary artery disease exist within the country, the incidence being extremely high in East Finland (province of North Karelia) (Karvonen *et al.*, 1970). Based on these facts, we studied the aggregation of coronary artery disease and of its main risk factors in the families of young men suffering from coronary artery disease in two areas, one (South Finland) with a moderate, and another (East Finland) with an exceptionally high incidence of coronary artery disease. In this report, results on the families of men with classical angina pectoris will be given. In

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subsequent reports, data on families of men with myocardial infarction, and an analysis of the South-East difference will be presented.

Subjects and methods

PROBANDS

The index patients with angina pectoris and their controls were obtained by screening the records of regular occupational health examinations carried out during 1970 to 1973 in large companies of the wood and paper industry having factories in both South Finland and East Finland. The records of about 6000 employees yielded 750 men aged 25 to 55 years who had abnormalities suggestive of coronary artery disease in the resting electrocardiogram (Minnesota Code Nos. 1·2–3, 4·1–3, 5·1–3, 6·1–2, 7·1–2 or 8·3)[1]. These men were examined by one of us (A.R.), and 106 of them (53 in each area) were judged to have definite angina pectoris with typical chest pain without evidence of previous myocardial infarction. Coronary artery disease had been diagnosed earlier in 70 men, and 22 had retired because of the disease. The duration of angina pectoris varied from 3 to 99 months. The age of the men ranged from 27 to 55 years with a mean of 49·0 years in the South and 49·5 years in the East.

For each angina pectoris proband, two prospective male controls matched for age and marital status were selected from the same occupational group. The candidate who at clinical examination was free of any symptoms suggestive of coronary artery disease, and whose date of birth was closest to that of the angina pectoris proband was chosen as a control. With respect to demographic characteristics examined, the angina pectoris and control probands appeared to be similar: about 90 per cent of both were born in the area of their present residence, and the birth years of their parents, their average family size, income, social class, and dietary habits were alike.

The probands underwent a clinical examination and a blood sample was obtained after an overnight fast. All the first-degree relatives were listed and consent was obtained to get in touch with these and to obtain the death certificates from any deceased family members. Two angina pectoris and 12 control probands were excluded from the study because they did not have at least 2 adult relatives who were available for the study. The small family size was not caused by coronary artery disease deaths in any of the families. Because of the large exclusion proportion among the control families it was decided not to apply matched pair analysis for the study. The exclusions did not change the average characteristics of the groups, however.

RELATIVES

The 198 probands (104 with angina and 94 controls) listed a total of 1571 first-degree relatives aged 15 years and over. Of these, 1143 were reported to be alive, 421 were deceased, and the status of 7 relatives was unknown. The living relatives were sent a questionnaire on their habits and diseases; they were also asked to visit the nearest laboratory to give a fasting blood sample. The laboratories were also asked to record the height, weight, and resting electrocardiogram (from relatives past 40) and to send the data and the serum sample to the Helsinki University Central Hospital. These data were obtained from 560 (92·1%) and 498 (93·1%) relatives of angina pectoris and control probands, respectively. The number of the participants is presented in Table 1. The age distribution of the relatives of the cases and of the controls were similar; the age of the living parents ranged from 54 to 86 years, that of the sibs from 19 to 69 years (mean 48·4 years), and that of the children from 15 to 35 years (mean 20·2 years) (Table 2).

Data from relatives

The questionnaires obtained from the relatives yielded information about previous diagnoses of coronary artery disease, myocardial infarction, hypertension, and diabetes, and about present medication, as well as about smoking habits and symptoms such as chest pain. Incomplete questionnaires were amended by personal mail and telephone contacts. The reported diagnoses of coronary artery disease were checked against records from a physician or hospital. To make the diagnoses of past myocardial infarction acceptable, evidence of unequivocal electrocardiographic abnormalities or diagnostic enzyme pattern was required: in other cases the diagnosis of coronary artery disease was accepted when the records described adequately the basis of the diagnosis. The reported diagnoses of diabetes and hypertension were accepted when treatment by a physician also was mentioned.

To evaluate the reliability of the questionnaire data and to collect information on the life changes that the occurrence of coronary artery disease in the family might have caused, a random sample of 102 relatives was examined by one of us (A.R.). The reporting of diagnosed coronary artery disease, hypertension, and diabetes appeared reliable. The

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[1] Minnesota Code numbers are:
1·2–3, nonspecific Q and QS changes.
4·1–3, ST depression with horizontal or downward ST segment.
5·1–3, negative or isoelectric T wave.
6·1–2, complete or partial 2° AV-block.
7·1–2, complete bundle-branch block.
8·3, atrial fibrillation or flutter.

Table 1 *Number of participants in study*

	South				*East*			
	Angina group		*Control group*		*Angina group*		*Control group*	
	Living	*Dead*	*Living*	*Dead*	*Living*	*Dead*	*Living*	*Dead*
Probands	51		48		53		46	
Relatives over age 14								
Fathers	3	43	7	40	4	49	4	39
Mothers	17	32	15	32	10	40	14	30
Brothers	64	26	49	12	81	25	63	20
Sisters	74	8	71	4	94	9	91	10
Sons	44	—	40	—	63	1	50	1
Daughters	38	—	36	—	68	—	58	—
Total relatives	240	109	218	88	320	124	280	100

Table 2 *Characteristics of study groups*

		South				*East*			
		Probands	*Brothers*	*Sisters*	*Children*	*Probands*	*Brothers*	*Sisters*	*Children*
Age (mean, years)	Angina	49·0	50·5	50·1	21·7	49·5	47·6	48·2	20·2
	Control	48·7	49·1	47·8	20·0	48·7	47·6	47·0	18·9
Body-mass index (mean, kg/m^2)	Angina	25·9	24·9	27·0	21·3	26·5	25·4	26·6	22·0
	Control	25·8	25·0	25·0	20·6	25·7	25·4	26·3	20·8
Regular smokers (%)†	Angina	60·8	46·1	26·8*	34·6	70·5	39·4	14·9	32·2
	Control	56·3	42·8	12·7	35·3	50·0	41·3	14·3	29·5
Hyperlipidaemic (%)‡	Angina	41·2*	31·3	35·1*	23·2*	52·8*	37·0	42·6*	22·1
	Control	12·5	20·4	15·5	13·1	19·5	33·3	25·3	16·7
Hypertensives (%)§	Angina	19·6*	12·3*	24·3	—	34·0*	24·7*	26·6	—
	Control	4·2	4·1	11·3	—	6·7	14·2	20·9	—
Diabetics (%)	Angina	7·8	4·6	4·3	—	7·5	2·5	2·5	—
	Control	—	—	4·2	—	—	—	2·2	—

*$P < 0·05$ for the difference between angina and control groups.

†Smoking before the diagnosis of coronary artery disease.

‡Hyperlipidaemia is defined as serum cholesterol greater than 8·3 mmol/l and/or serum fasting triglyceride level greater than 2·15 mmol or 1·90 mmol/l in men and women, respectively. The values are adjusted to age 45.

§Hypertension and diabetes diagnosed by measurement in probands and by questionnaire in relatives. Glucose tolerance not determined.

agreement of the responses to the questionnaire with those given at the clinical examination was over 90 per cent. The agreement in reporting smoking habits was over 80 per cent, but for chest pain and other symptoms it was only about 40 per cent. Therefore, symptoms reported in the questionnaire were not used at all in the study. Though the relatives of the diseased expressed increased concern about their health, this did not appear to have led to any major changes in their dietary or smoking habits, neither did the frequency of the visits to physicians increase. Thirty-five per cent of the relatives who themselves had coronary artery disease smoked less than before the diagnosis of coronary artery disease, but other life changes were negligible.

The causes of death of the deceased relatives were registered from death certificates which were available for 93 per cent of the cases. To avoid the bias caused by changes in the nomenclature in earlier editions of International Classification of Diseases (ICD), the primary cause of death was recoded according to the latest (1965) revision of ICD in the Central Statistical Office of Finland.

The electrocardiograms were coded by an experienced technician using the Minnesota Code. Every sixth recording was read also by a second technician. The agreement between the readers was excellent.

ANALYSIS OF SERUM LIPIDS

Serum cholesterol was determined by the method of Huang *et al.* (1961) and serum triglycerides by an autoanalyser according to Kessler and Lederer (1965). The coefficient of variation of the determinations during the 2-year period of the study did not exceed 3 per cent. To minimise the effect of seasonal variation of the lipid (Aromaa *et al.*, 1975), the sampling was discontinued for the summer months.

All lipid values were age-adjusted using regression equations derived from a large Finnish population study (Aromaa *et al.*, 1975). The cutting point for definition of hyperlipidaemia was set at the 90th centile of the control relatives after adjustment to age 45. These limits are 320 mg/100 ml (8·3 mmol/l) for serum cholesterol in both sexes and 2·15 mmol/l and 1·90 mmol/l for serum triglycerides in men and women, respectively. These values are close to the 90th centile values of the middle-aged population in Finland (Aromaa *et al.*, 1975) and close to the 95th centile limits used in USA (Goldstein *et al.*, 1973). Classification of hyperlipidaemia was made on the basis of WHO recommendation (Beaumont *et al.*, 1970).

DEFINITIONS AND METHODS OF ANALYSIS OF DATA

The following criteria of familial aggregation were used in this study. Familial hyperlipidaemia was considered to be present when at least 30 per cent (and a minimum of 2) of the members of a family had hyperlipidaemia. The term familial hypertension was used when at least 30 per cent (and a minimum of 2) of the adult members in a family had clinically diagnosed hypertension. Familial aggregation of coronary artery disease was believed to be present when at least 2 members (excluding the proband) had developed a documented coronary artery disease before the age of 65.

Life tables were constructed according to the method of Cutler and Ederer (1958) using intervals of 5 years. The relatives entered the tables at the age of 30, and they were withdrawn at the end of 1974 or at the age of their death, if it had occurred before that date. Life tables were constructed for mortality from all causes, from all cardiovascular causes (ICD Code Nos 400–450), and from coronary artery disease (Nos 410–413). In addition, combined coronary artery disease morbidity and mortality was evaluated by making the occurrence of nonfatal coronary artery disease analogous to coronary artery disease death. The living affected relatives were withdrawn at the age of the first diagnosis of coronary artery disease. The significance tests for the life tables were calculated according to Mantel (1966). Qualitative data were analysed by Fisher's exact test and χ^2 test with Yates' correction. For continuous data, Student's t test was used. Since the values of the sibs and children within a family are not independent of each other, significance tests will have to be interpreted as rough estimates of strength of association between the variables.

Results

CORONARY ARTERY DISEASE IN RELATIVES

Parents

The mortality of the fathers from the South and the East was nearly equal. In both areas, the proportion of fathers who had died from cerebrovascular diseases and from coronary artery disease was 1·5 and 2 times greater, respectively, for fathers of cases than for fathers of controls. The mortality from all causes was similar among fathers of cases and controls, however. Curves of the cumulative probability of dying for the combined southern and eastern groups are presented in Fig 1. The risk of the fathers of cases dying from coronary artery disease by the age of 65 was approximately 25 per cent, which was 5 times greater than the corresponding risk for control fathers. There were no differences in total, cardiovascular disease, or coronary artery disease mortality between the mothers of angina pectoris and control probands, or between the case mothers in the two areas.

Sibs

The occurrence of clinical coronary artery disease among the sibs of angina pectoris probands and controls is shown in Table 3. Both fatal and nonfatal myocardial infarction as well as angina pectoris were significantly more common among sibs of cases than among sibs of controls. The cumulative probability of developing coronary artery disease is presented in Fig 2. The risk of fatal or nonfatal coronary artery disease before the age of 65 was much higher for the brothers of cases than

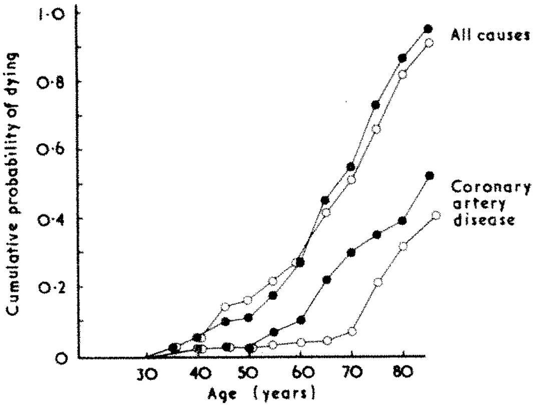

Fig. 1 *Cumulative probability of dying from all causes and from coronary artery disease for fathers of angina pectoris probands (●) and controls (○).*

Table 3 *Prevalence of diagnosed coronary artery disease in sibs aged 30 to 64 of patients with angina pectoris and of age-matched controls*

Group	*Myocardial infarction fatal or nonfatal (%)*	*Angina pectoris (%)*	*All coronary heart disease (%)*
South			
Case sibs	9·1*	8·4*	17·5*
Control sibs	0·8	2·4	3·2
East			
Case sibs	11·2*	15·5*	26·7*
Control sibs	1·9	6·3	8·2

*P < 0·01 for the difference between sibs of patients and controls.

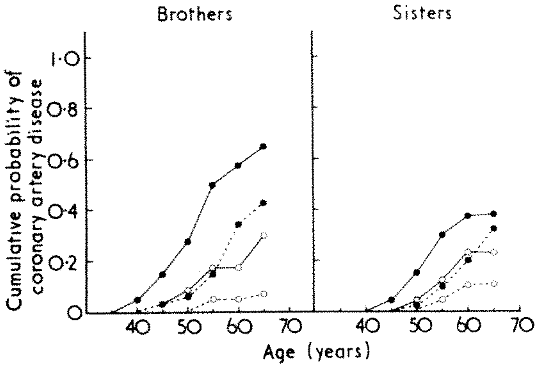

Fig. 2 *Cumulative probability of fatal or nonfatal coronary artery disease for brothers and sisters of angina pectoris probands (●) and controls (○) in South Finland (– – –) and East Finland (——).*

for those of controls, with the cumulative probabilities of 52 per cent versus 5 per cent and 65 per cent versus 31 per cent in the South and East, respectively.

The sisters of angina pectoris probands showed a much increased risk of coronary artery disease. By the age of 65, sisters of cases in both areas had 35 per cent probability of developing coronary artery disease, while the corresponding values for control sisters were 11 per cent in the South and 23 per cent in the East.

Electrocardiographic abnormalities

Ischaemic electrocardiographic abnormalities were significantly more common in the relatives of angina pectoris probands than in control relatives (Table 4). The difference in the prevalence of ischaemia was threefold also among the relatives who were free of clinical coronary artery disease. Signs of probable old myocardial infarction (Minnesota Code 1·1, 1·2+5·1, or 1·2+5·2) were present in 3·0 per cent of the sibs of angina pectoris probands and in 0·5 per cent of the sibs of controls. Unexpectedly, no regional differences were found in the frequency of electrocardiographic abnormalities in symptom-free relatives.

FAMILIAL AGGREGATION OF CORONARY ARTERY DISEASE

There was a distinct clustering of coronary artery disease in the families of the angina patients (Table 5). In 30 per cent of the case families in the East and in 23 per cent of the case families in the South, at least 2 members in addition to the proband had developed clinical coronary artery disease before the age of 65. None of the control families in the South and 7 per cent of control families in the East showed a similar aggregation of coronary artery disease. The aggregation was found mostly in sibs. Approximately 50 per cent of the angina patients had at least one sib who had manifested clinical coronary artery disease.

Table 4 *Prevalence of ischaemic changes in resting electrocardiogram in relatives over age 40 of patients with angina pectoris and of controls*

Group		*All relatives (%)*	*Relatives without clinical coronary artery disease (%)*
Parents	Angina	54·3	56·5
	Control	41·0	32·3
Brothers	Angina	18·3*	10·1
	Control	5·1	4·4
Sisters	Angina	24·6*	17·7*
	Control	9·2	5·3

Minnesota Code 1·1–3, 4·1–3, 5·1–2.
*P < 0·01 for the difference between relatives of angina and control groups.

Table 5 *Distribution of coronary artery disease in families of patients with angina pectoris and of controls (index excluded)*

No. of relatives under age 65 with coronary artery disease per family	*South*		*East*	
	Case families (%)	*Control families (%)*	*Case families (%)*	*Control families (%)*
0	52·9	81·3	32·1	63·1
1	23·5	18·7	37·7	30·4
2	19·6	—	17·0	6·5
3	3·9	—	13·2	—

*Fatal and nonfatal coronary artery disease
P < 0·001 between the Southern case and control families.
P < 0·005 between the Eastern case and control families.

Multiple cases of coronary artery disease among the sibs of the angina pectoris probands were found in one-sixth of the southern and in one-quarter of the eastern families, while a similar clustering occurred in only 3 of 94 control families.

AGGREGATION OF CORONARY RISK FACTORS IN FAMILIES OF PROBANDS

Hyperlipidaemia

Raised serum lipids were detected in 41 per cent of the southern and in 53 per cent of the eastern angina pectoris probands, which denotes an almost threefold increase over the rate in the control probands. The prevalence of hyperlipidaemia was distinctly increased also among the relatives of the angina pectoris probands (Table 2). While no regional differences existed in the prevalence of pure hypertriglyceridaemia, hypercholesterolaemia, often associated with slightly raised serum triglyceride levels, was more common in the East (21·9 vs. 13·2 per cent in the relatives of cases, $P < 0{\cdot}01$, and 15·0 vs. 8·2 per cent in the relatives of controls, $P < 0{\cdot}05$). Familial hyperlipidaemia was present in 49 per cent of the southern and in 62 per cent of the eastern angina pectoris families (difference statistically not significant) as well as in 13 per cent of the southern and in 39 per cent of the eastern control families ($P < 0{\cdot}02$) (Table 6). While there were no pronounced differences in the prevalences of pure forms of familial hyperlipidaemia, the prevalence of multiple-type (combined) familial hyperlipidaemia was 3 times greater in the angina pectoris families than in the control families. Furthermore, familial hyperlipidaemias, especially the multiple-type abnormality, were more common in both case and control families in the East than in the South. It is remarkable that most hypercholesterolaemic relatives came from families with multiple-type familial hyperlipidaemia.

Table 6 *Prevalence of familial hyperlipidaemia in families of patients with angina pectoris and of controls (probands included)*

Group	*All familial hyperlipidaemia*	*Per cent of families*		
		Type II	*Type IV*	*Multiple type*
Case families South	49·0	9·8	7·8	31·4
Control families South	12·8	6·4	2·1	4·3
Case families East	62·3	13·2	3·8	45·3
Control families East	39·1	13·0	6·5	19·6

Hypertension

Hypertensive disease was 5 times more common in the angina pectoris probands than in their controls. The frequency of hypertension was increased also among the members of the families of the angina pectoris probands (Table 2). Familial aggregation of hypertension was present in one-tenth of the southern and in one-quarter of the eastern case families. The rate was approximately twice as great as among the control families in each area. There was no association between the occurrence of familial hyperlipidaemia and hypertension. The two conditions coincided in one southern and in six eastern case families which is not more than would be expected by chance association alone.

ASSOCIATION OF FAMILIAL HYPERLIPIDAEMIA AND HYPERTENSION WITH FAMILIAL CORONARY ARTERY DISEASE

The occurrence of hyperlipidaemia, hypertension, and clinical diabetes in the families with different patterns of coronary artery disease are shown in Table 7. There was a stepwise increase in the prevalence of each of the three risk factors in the coronary artery disease-free members of families with none, one, or several cases of coronary artery disease. Thus, sibs without clinical coronary artery disease but belonging to a family with many cases of

Table 7 *Prevalence of coronary artery disease risk factors in relation to the familial aggregation of coronary artery disease*

*Group**	*Hyperlipidaemia (%)*	*Hypertension (%)*	*Hyperlipidaemia and hypertension (%)*	*Clinical diabetes (%)*
Sibships without coronary artery disease (62)	15·1	8·1	5·9	0·5
Sibships with one case of coronary artery disease (which is excluded) (51)	34·5	13·5	6·8	2·0
Sibships with multiple cases of coronary artery diseases (48)				
Sibs without coronary artery disease	37·9	25·3	10·5	3·2
Sibs with coronary artery disease	42·9	42·9	23·8	7·9

*Families with proband and at least one available sib over 30 years.
The number of families in each category in parentheses.

coronary artery disease had 2·5 times more hyperlipidaemia, 3·1 times more hypertension, and 6·4 times more clinical diabetes than the members of families without any diagnosed case of coronary artery disease. The risk of familial coronary artery disease was only slightly increased in the case families with familial hyperlipidaemia or hypertension (relative risks 1·1 and 1·7, respectively). The risk was, however, more than doubled in the families where the two traits coincided. In these families, more than one-half of the sibs aged 30 to 65 had already developed clinical coronary artery disease.

OTHER RISK FACTORS

Smoking was more common among the angina pectoris probands than among the control probands, but the smoking habits of the relatives were similar in all groups (Table 2). Furthermore, smoking did not show any familial clustering in this study. There was a 1·7-fold increase in the coronary artery disease rate among the present or former heavy smokers as compared with that among the non-smokers. The distribution of body weights of the cases and controls as well as of their relatives were similar (Table 2). In all groups, about 30 per cent of the women and 10 per cent of the men exceeded their desirable weight by at least 20 per cent. Obesity did not show familial trends in this material.

Discussion

Family studies based on interviews of affected probands or their relatives have often been criticised because the patients, as well as their relatives, are more aware of the disease and its manifestations in their families, and are also more prone to report it than are the controls.

To reduce this bias in the present study, all information on cardiovascular disease was verified from physician or hospital records or from death certificates. Strict criteria were also applied in accepting a positive diagnosis of coronary artery disease. Though this procedure eliminates only a fraction of all biases inherent in family studies (Murphy, 1967), most false positives are eliminated, sometimes at the expense of missing some true positives.

In spite of these measures, the families of patients with angina pectoris showed a considerably higher rate of coronary artery disease than those of controls. This finding is consistent with the results obtained in earlier studies, which were based on reports of history of coronary artery disease in the relatives of cases and controls (Gertler and White, 1954; Thomas and Cohen, 1955; Rose, 1964; Phillips *et al.*, 1974) or on analysis of parent-child (Oscherwitz *et al.*, 1968; Deutscher *et al.*, 1970; Hammond *et al.*, 1971) or twin (Harvald and Hauge, 1970; Liljefors, 1970; de Faire, 1974) pairs. The excess risk of coronary artery disease mortality observed among fathers of probands with angina pectoris is similar to that shown in other studies (Gertler and White, 1954; Thomas and Cohen, 1955; Shanoff *et al.*, 1961; Rose, 1964; Slack and Evans, 1966; Phillips *et al.*, 1974). Also, the lack of excessive mortality from coronary artery disease among case mothers has been reported by other investigators (Gertler and White, 1954; Thomas and Cohen, 1955; Phillips *et al.*, 1974). Our results fail, however, to convey any increase in the rate of cerebrovascular accidents in mothers, which has been suggested by Phillips *et al.* (1974). The frequency of coronary artery disease among the sibs of affected probands has consistently been reported to be raised, though the actual rates have varied considerably (Gertler and White, 1954; Shanoff *et al*, 1961; Rose, 1964; Slack and Evans, 1966; Phillips *et al.*, 1974). The risk of coronary artery disease for the brothers of the probands with angina pectoris in this study was close to the 5-fold increase in risk of coronary artery disease death for the brothers of affected men under 55, which was reported from life table analysis by Slack and Evans (1966). In their series the heritability of liability to coronary artery disease in the brothers of affected men aged 35 to 64 was 60 per cent when determined by the principle of Falconer (1965). The same method would give a heritability estimate of 80 per cent in the present study. Both values are close to 100 per cent, which would characterise a condition completely determined by additive polygenic inheritance. It is likely that most of the difference between the two estimates could be explained by the differences in the age structure of the probands and perhaps in part by the difference in the clinical forms of coronary artery disease of the probands.

Classical angina pectoris in young men is usually as indicative of advanced obstructive coronary atherosclerosis as are other manifestations of coronary artery disease (e.g. myocardial infarction or cardiac death) (Fuster *et al.*, 1975). If associated with electrocardiographic changes, as in the present study, angina pectoris is even more likely to represent an advanced stage of severe, obstructive atherosclerosis. Some twin studies (Cederlöf *et al.*, 1967; Liljefors, 1970) and parent-child analyses (Sholtz *et al.*, 1975) have suggested that the genetic influence in the angina pectoris syndrome is equal to or even greater than in other manifestations of coronary artery disease. In unpublished studies we have noted that though there are differences between the predominant clinical forms of coronary artery disease in the families of angina pectoris and myocardial infarct probands, the total aggregation of clinical coronary artery disease is similar in the two groups. Asymptomatic forms of coronary artery disease appear, in fact, to be more common in the families of probands with angina pectoris.

Familial aggregation of coronary artery disease may be based on genetic factors but it is difficult to separate these from the influences of a common environment and traditions shared by family members. All major risk factors such as serum lipid levels (Schaefer *et al.*, 1958; Heiberg, 1974), arterial blood pressure (Miall and Oldham, 1963; Zinner *et al.*, 1971) and blood sugar (Deutscher *et al.*, 1970) are likely to be under polygenic control. Monogenic familial hypercholesterolaemia is a rare disorder and, in spite of its high atherogenicity (Stone *et al.*, 1974), it can account for a very minor fraction of the genetic component of coronary artery disease. In contrast, the polygenically determined milder forms of both hyperlipoproteinaemia and hypertension with heritability estimates of the order of 0·30 for each (Schaefer *et al.*, 1958; Miall and Oldham, 1963), could be solely responsible for most of the observed aggregation of coronary artery disease.

Many of the findings of the present study lend support to the overwhelmingly important role of these two risk factors. In particular, the high prevalence of coronary artery disease in the eastern control families was associated with high rates of both hyperlipidaemia and hypertension, whereas both coronary artery disease and the two risk factors were consistently low in the southern control families. Furthermore, the difference in the rates of the risk factors between South and East diminished considerably at such high frequency of coronary artery disease as was noticed in case families. In addition, the coexistence of familial hyperlipidaemia and hypertension was always associated with much increased rate of coronary artery disease in the family. Likewise, in families with increased aggregation of coronary artery disease, the prevalence of both risk factors was increased among the family members who as yet had shown no evidence of coronary artery disease. Though these observations do not provide cogent proof of causality, it appears that most of the observed difference in the frequency of coronary artery disease between case and control families, as well as of that between the control families in the South and East, could be explained by variations in the rate of these two major risk factors. It is difficult, however, to estimate from our data the possibly different contribution of these risk factors to coronary artery disease in the two areas.

It is likely that as well as the already mentioned risk factors, others operate in the families of the present study. We found smoking to be an independent risk factor even in the presence of familial hyperlipidaemia or hypertension. A similar conclusion has been drawn earlier from families affected with familial hypercholesterolaemia (Stone *et al.*, 1974). The rapid increase of smoking in Finland since the 1930s, superimposed on the atherogenic genes, may, in fact, be a major determinant in the well-documented and pronounced secular increase in the rate of coronary artery disease that was also seen between the generations of fathers and their offspring in the present study.

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References

Aromaa, A., Björkstén, F., Eriksson, A. W., Maatela, J., Kirjarinta, M., Fellman, J., and Tamminen, M. (1975). Serum cholesterol and triglyceride concentrations of Finns and Finnish Lapps. 1. Basic data. *Acta Medica Scandinavica*, **198**, 13–22.

Beaumont, J. L., Carlson, L. A., Cooper, G. R., Fejfar, Z., Fredrickson, D. S., and Strasser, T. (1970). Classification of hyperlipidaemias and hyperlipoproteinaemias. *Bulletin of the World Health Organization*, **43**, 891–908.

Cederlöf, R., Friberg, L., and Jonsson, E. (1967). Hereditary factors and 'angina pectoris'. A study on 5877 twin-pairs with the aid of mailed questionnaires. *Archives of Environmental Health*, **14**, 397–400.

Cutler, S. J., and Ederer, F. (1958). Maximum utilization of the life table method in analyzing survival. *Journal of Chronic Diseases*, **8**, 699–712.

de Faire, U. (1974). Ischaemic heart disease in death discordant twins. *Acta Medica Scandinavica*, Suppl. 568.

Deutscher, S., Ostrander, L. D., and Epstein, F. H. (1970). Familial factors in premature coronary heart disease—a preliminary report from the Tecumseh community health study. *American Journal of Epidemiology*, **91**, 233–237.

Epstein, F. H., and Krueger, D. E. (1969). The changing incidence of coronary heart disease. In *Modern Trends in Cardiology*, **2**, p. 17. Ed. by A. Morgan Jones. Butterworths, London.

Falconer, D. S. (1965). The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Annals of Human Genetics*, **29**, 51–71.

Fuster, V., Frye, R. L., Connolly, D. C., Danielson, M. A., Elveback, L. R., and Kurland, L. T. (1975). Arteriographic patterns early in the onset of the coronary syndromes. *British Heart Journal*, **37**, 1250–1255.

Gertler, M. M., and White, P. D. (1954). *Coronary Heart Disease in Young Adults; A Multidisciplinary Study.* Harvard University Press, Cambridge, Massachusetts.

Goldstein, J. L., Schrott, H. G., Hazaard, W. R., Bierman, E. L., and Motulsky, A. G. (1973). Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new injerited disorder, combined hyperlipidemia. *Journal of Clinical Investigation,* **52,** 1544–1568.

Hammond, E. C., Garfinkel, L., and Seidman, H. (1971). Longevity of parents and grandparents in relation to coronary heart disease and associated variables. *Circulation,* **43,** 31–44.

Harvald, B., and Hauge, M. (1970). Coronary occlusion in twins. *Acta Geneticae Medicae et Gemellologiae,* **19,** 248–250.

Heiberg, A. (1974). The heritability of serum lipoprotein and lipid concentrations. A twin study. *Clinical Genetics,* **6,** 307–316.

Huang, T., Chen, C., Wefler, V., and Raftery, A. (1961). A stable reagent for the Liebermann-Burchard reaction. Application to rapid serum cholesterol determination. *Analytical Chemistry,* **33,** 1405–1406.

Karvonen, M. J., Orma, E., Punsar, S., Kallio, V., Arstila, M., Luomanmäki, K., and Takkunen, J. (1970). Coronary heart disease in seven countries. VI. Five-year experience in Finland. *Circulation,* **41-42,** Suppl. 1, 52–62.

Kessler, G., and Lederer, H. (1965). Fluorometic measurement of triglycerides. In *Automation in Analytical Chemistry, Technicon Symposium,* p. 341. Ed. by L. T. Skeggs, Jr. Mediad, New York.

Liljefors, I. (1970). Coronary heart disease in male twins. Hereditary and environmental factors in concordant and discordant pairs. *Acta Medica Scandinavica,* Suppl. 511.

Mantel, N. (1966). Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports,* **50,** 163–170.

Miall, W. E. (1971). Heredity and hypertension. *Practitioner,* **207,** 20–27.

Miall, W. E., and Oldham, P. D. (1963). The hereditary factor in arterial blood-pressure. *British Medical Journal,* **1,** 75–80.

Murphy, E. A. (1967). Some difficulties in the investigation of genetic factors in coronary artery disease. *Canadian Medical Association Journal,* **97,** 1181–1192.

Nevanlinna, H. R. (1972). The Finnish population structure. A genetic and genealogical study. *Hereditas,* **71,** 195–236.

Nikkilä, E. A., and Aro, A. (1973). Family study of serum lipids and lipoproteins in coronary heart-disease. *Lancet,* **1,** 954–959.

Oscherwitz, M., Krasnoff, S. O., Moretti, L., and Syme, S. L. (1968). The relationship of myocardial infarction to parental mortality and longevity. *Journal of Chronic Diseases,* **21,** 341–348.

Phillips, R. L., Lilienfeld, A. M., Diamond, E. L., and Kagan, A. (1974). Frequency of coronary heart disease and cerebrovascular accidents in parents and sons of coronary heart disease index cases and controls. *American Journal of Epidemiology,* **100,** 87–100.

Rose, G. (1964). Familial patterns in ischaemic heart disease. *British Journal of Preventive and Social Medicine,* **18,** 75–80.

Schaefer, L. E., Aldersberg, D., and Steinberg, A. G. (1958). Heredity, environment, and serum cholesterol. A study of 201 healthy families. *Circulation,* **17,** 537–542.

Shanoff, H. M., Little, A., Murphy, E. A., and Rykert, H. E. (1961). Studies of male survivors of myocardial infarction due to 'essential' atherosclerosis. I. Characteristics of the patients. *Canadian Medical Association Journal,* **84,** 519–530.

Sholtz, R. I., Rosenman, R. H., and Brand, R. J. (1975). The relationship of reported parental history to the incidence of coronary heart disease in the Western Collaborative Group Study. *American Journal of Epidemiology,* **102,** 350–356.

Slack, J., and Evans, K. A. (1966). The increased risk of death from ischaemic heart disease in first degree relatives of 121 men and 96 women with ischaemic heart disease. *Journal of Medical Genetics,* **3,** 239–257.

Stone, N. J., Levy, R. I., Frederickson, D. S., and Verter, J. (1974). Coronary artery disease in 116 kindred with familial type II hyperlipoproteinemia. *Circulation,* **49,** 476–488.

Tattersall, R. B., and Fajans, S. S. (1975). A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes,* **24,** 44–53.

Thomas, C. B., and Cohen, B. H. (1955). The familial occurrence of hypertension and coronary artery disease, with observations concerning obesity and diabetes. *Annals of Internal Medicine,* **42,** 90–127.

Zinner, S. H., Levy, P. S., and Kass, E. H. (1971). Familial aggregation of blood pressure in childhood. *New England Journal of Medicine,* **284,** 401–404.

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Studies of correlation between progression of coronary artery disease, as assessed by coronary arteriography, left ventricular end-diastolic pressure, ejection fraction, and employability

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The occupational status of a group of 100 male patients, 35 to 68 years of age, with chronic ischaemic heart disease was studied, and related to the severity and distribution of coronary artery stenosis seen on the arteriograms and to left ventricular function. In this series of patients 31 per cent were working, 31 per cent were recorded as temporarily sick, and 38 per cent as permanently disabled.

It appears that while the type of previous occupation and physical activity associated with the job were of importance, there was no correlation between employability on the one hand and severity and distribution of coronary artery disease on the other.

'Blue-collar' workers had a higher rate of unemployment than those in 'white collar' occupations, but this could not be explained by differences in severity of coronary artery disease.

The first report on the resumption of work in patients with ischaemic heart disease was published in 1930 (Conner and Holt). Since then, the re-employment of patients with coronary artery disease has been discussed frequently and several variables have been used with the view to predicting the possibility of occupational rehabilitation. According to Garrity (1973), these variables may be classified into three categories: *sociodemographic, sociopsychological,* and *medical.* Most previous studies have been undertaken with the two former categories as their central theme. The re-employment of patients with ischaemic heart disease must also depend on the severity of coronary artery disease itself, though an extensive review of the published material on cardiac rehabilitation indicates that very little research has been done in this field. This is particularly true in the time of the chronic phase, when many patients are dependent on social security systems.

In the present study, attention has been focused upon the correlation between the working status and objective signs of disease, as progression of disease seen in coronary arteriograms, together with data for left ventricular function.

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Patients and methods

The study population was a group of 100 male patients, 35 to 68 years in age (mean = 52·7 years) who had chronic, stable, and arteriographically documented coronary artery disease. They were referred to us for diagnostic evaluation before aortocoronary vein bypass surgery. According to the working status at admission, the patients were divided into 3 subgroups.

Actually working, i.e. all patients who at the time of admission were working more than 4 hours a day.

Temporary disability, i.e. those not working at the time of admission, but where their condition was assumed to be temporary ('temporary sick-leave').

Permanent disability, i.e. those not working at the time of admission, and where their condition was assumed to be permanent.

On admission, the patients were interviewed by professional social workers (T.B. and A.S.). The patients were classified according to their occupational status. The largest occupational group, 'blue collar' workers, consists of all skilled and unskilled manual labourers. The second group, 'white collar' workers, was composed of managerial, middle, and lower status 'white collar' occupations and included also self-employed businessmen and professionals. The sociomedical examination also included an assessment of physical and psychological stress involved in the work, based on the patients' own judgment. According to this, the patients were classified into three categories: heavy, moderate, and light physical strain, and severe, moderate, and no psychological stress.

Selective coronary arteriography was performed by the technique of Judkins (1967). The three main coronary arteries—the anterior descending branch and the circumflex branch of the left coronary artery and the right coronary artery were identified and evaluated separately. Each artery was graded individually according to the following scoring system. 0, no arteriographic abnormalities; 1, localised narrowing estimated to be more than 10 per cent but less than 75 per cent of the luminal cross-section area; 2, narrowing(s) estimated to be more than 75 per cent but less than 90 per cent; 3, total occlusion without any filling of the distal segment from the proximal portion. The 3 scores together gave a total score which represented the overall obstructive disease for all 3 arteries of the heart. Left ventriculography was performed in the right anterior oblique plane. The contrast material used was Isopaque Coronar (metrizoate meglumine/Na/Ca (58/9/1) 370 mg J/ml).

Left ventricular pressures were measured before and 2 minutes after left ventriculography. Pressures were recorded with Elema Schønander equipment (Transducer EMT 35 and Mingograf 81). The baseline was at the 4th intercostal space on the anterior axillary line. The end diastolic pressure was measured at the intercept between the 'a' wave and the rapid ventricular upstroke.

The films were analysed directly on a Tagarno projector. The ejection fraction was measured by outlining the internal contour of the left ventricle in systole and diastole; the formula given by Arbogast *et al.* (1973) was used. The validity of this mathematical model in man has been shown by Davila and Sanmarco (1966).

The data were processed at the hospital computer centre. The P value indicated in the Tables refers to the significance level of the classical χ^2 test of independence between two categorical variables.

Results

At admission, 31 patients were recorded as working while 31 were recorded as temporarily sick and 38 as permanently disabled. Table 1 shows the interrelation between working status and age, duration of symptoms, occupation, physical strain, and psychological stress in previous occupation. In these series of men under 68 years, age *per se* apparently was not related to working status. Though there was no significant correlation between working status and duration of symptoms, the data indicate a tendency towards a higher rate of unemployment among those with the longest duration of symptoms. More obvious, the data show that working status was closely dependent on the type of previous employment and the physical strain associated with it. 'Blue collar' workers had a higher rate of unemployment than 'white collar' workers or employers. Similarly, those with jobs containing heavy or moderate physical stress had a higher rate of unemployment than those with less physically stressful occupations. On the other hand, the psychological stress involved in a job was apparently unrelated to work status.

Analysis of data obtained from the coronary arteriograms showed that no correlation seemed to exist between work status on the one hand and severity of coronary artery disease on the other.

Table 1 *Relations between working status and age, duration of symptoms, occupation, physical strain, and psychological stress in previous occupation*

	Employed at time of examination *(31)* %	*Temporarily sick* *(31)* %	*Permanently disabled* *(38)* %	*Total*
Age (y)				
30–49	50	0	50	6
40–49	26	30	43	23
50–59	39	29	37	52
60–69	21	47	32	19
				P: 0·43
Duration of symptoms (y)				
< 1	47	47	7	15
1–5	27	35	38	52
> 5	30	18	52	33
				P: 0·09
Occupational category				
Blue collar	15	36	48	66
White collar	62	21	17	34
				P: 0·01
Physical strain involved in previous work				
Heavy	19	29	52	42
Moderate	24	41	35	37
Easy	65	20	15	21
				P: 0·01
Psychological stress involved in previous work				
Severe	36	29	36	28
Moderate	31	44	26	39
None	27	18	55	33
				P: 0·11

The results were the same whether the scores of each main coronary artery were analysed separately or the total scores were used (Table 2). Analysis of the haemodynamic pattern and work status showed that the left ventricular function estimated from the ejection fraction and the left ventricular end diastolic pressures before and after ventriculography were the same when working and non-working patients were compared (Table 3).

In the present study 'blue collar' workers had a higher rate of unemployment than those in 'white collar' occupations. 'Blue collar' workers had the same age distribution as the 'white collar' group, they were more often engaged in heavy physical work, and they more often belonged to lower social strata than those from 'white collar' occupations. No differences were found between 'white' and 'blue collar' groups in psychological stress associated with their previous work (Table 4). There was no apparent difference between the groups in relation to the severity of coronary artery disease present (Table 5).

Table 3 *Relations between working status and left ventricular function estimated from ejection fraction and left ventricular end diastolic pressures (LVED) before and after ventriculography*

	Employed at time of examination *(31)* %	*Temporarily sick* *(31)* %	*Permanently disabled* *(38)* %	*Total*
Ejection fraction				
> 50 per cent	31	33	36	84
< 50 per cent	31	19	50	16
				P: 0·44
LVED pressure before ventriculography				
12 mmHg	31	28	42	36
12–24 mmHg	28	37	35	54
25 mmHg or more	50	10	40	10
				P: 0·44
LVED pressure after ventriculography				
< 12 mmHg	20	40	40	15
12–24 mmHg	30	30	39	56
25 mmHg or more	38	28	34	29
				P: 0·79

Table 2 *Relations between working status and scores in anterior descending artery (LAD), circumflex artery, and right coronary artery*

Coronary arteriogram	*Employed at time of examination* *(31)* %	*Temporarily sick* *(31)* %	*Permanently disabled* *(38)* %	*Total*
Score in anterior descending artery (LAD)				
Open	29	47	24	17
10–75 per cent	18	35	47	17
75–90 per cent	42	27	30	33
Occluded	27	24	48	33
				P: 0·18
Score in circumflex artery				
Open	31	31	38	32
10–75 per cent	18	36	46	28
75–90 per cent	39	26	35	31
Occluded	44	33	22	9
				P: 0·73
Score in right coronary artery				
Open	38	29	33	21
10–75 per cent	17	67	17	12
75–90 per cent	28	34	38	32
Occluded	34	17	49	35
				P: 0·13
Total score				
1–5	27	45	27	11
6–8	31	31	38	13
9–11	30	39	30	23
12 and more	32	25	43	53
				P: 0·78

Table 4 *Relations between type of previous occupation and age, physical strain, psychological stress involved in previous work, and social strata*

	Manual labourers ('blue collar') *(66)* %	*Employees and owners and managers ('white collar')* *(34)* %
Age (y)		
30–39	6	6
40–49	20	23
50–59	55	52
60–69	20	19
Total	101	100
		P: 0·10
Physical strain involved in previous work		
Heavy	50	42
Moderate	38	37
Easy	12	21
Total	100	100
		P: 0·01
Psychological stress involved in previous work		
Severe	21	28
Moderate	41	39
None	38	33
Total	100	100
		P: 0·44
Social strata		
Above average	3	16
Average	91	79
Below average	6	5
Total	100	100
		P: 0·00

Table 5 *Relations between type of previous occupation and total coronary artery score*

Coronary arteriogram	*Manual labourers* *(66)* %	*Employees and owners and managers* *(34)* %
Total score		
1–5	9	11
6–8	14	13
9–11	21	23
12 and more	56	53
Total	100	100
		P: 0·74

Discussion

The employability of patients with ischaemic heart disease has previously been based mostly on studies carried out after an acute myocardial infarct and from the point of view of number of infarctions, clinical heart failure, duration of sick leave, age, sex, marital status, and previous occupation. The present research is based on patients with chronic ischaemic heart disease of whom the majority had been dependent on social security systems for a long time, and grew out of the awareness that the work status in such patients should be related to the extent of structural involvement seen from the coronary arteriograms and patterns of left ventricular function.

Our results indicate that unemployment in patients with chronic ischaemic heart disease cannot be explained by the apparent severity of the coronary artery disease. The extent of structural changes seen on the coronary arteriograms as well as various tests of left ventricular performance were found to be identical when the patients working full time were compared with those recorded as temporarily sick or permanently disabled. The employability of patients with chronic ischaemic heart disease seems to be burdened with a discrepancy between the employability on the one hand and the objective indices of heart disease on the other. This conclusion is in accordance with other investigations, studying rehabilitation after heart valve operations (Nitter-Hauge *et al.,* 1976).

The tendency observed in the present study parallels that seen in cases of patients who abandon work after an acute myocardial infarct (Malmcrona *et al.,* 1962; Sharland, 1964; Shapiro *et al.,* 1972; Vuopala, 1972). The type of work done previously by the patients seems to be a major determinant in deciding whether they will be able to return to it. The prospects are usually less favourable for 'blue collar' than for 'white collar' workers. It is also known that after an acute myocardial infarct, the relative discrepancy in occupational prognosis by severity of the illness diminishes with time and is relatively small after one or two years (Weinblatt *et al.,* 1966; Kjøller, 1976). It is interesting to note that according to Kjøller (1976) only 37 per cent of patients unemployed after a myocardial infarct gave cardiac symptoms as the main factor why they had not gone back to work. It was claimed equally often that work was abandoned voluntarily or on account of an illness other than heart disease. In addition, in 19 per cent of the cases the main reason was that a general practitioner in the course of a routine check-up had advised the patients to abandon work. The influence of casual advice from general practitioners, the reluctance of employers to allow 'blue collar' workers to resume their previous work, the possible inhibiting role of workmen's compensation rulings and disability pensions, and the relative inflexibility of some 'blue collar' jobs in offering less strenuous work routines could also contribute to the differences observed in employability in the present study.

Because of methodological problems, the occupational circumstances of the present patients cannot be fully assessed. From the arteriographic and haemodynamic findings, however, it is tempting to suggest that many of those recorded as unemployed should be fit for some form of work.

More extensive examinations including coronary arteriography and evaluation of the type of work should be used before definite conclusions regarding working ability are made.

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References

Arbogast, R., Solignac, A., and Bourassa, M. G. (1973). Influence of aortocoronary saphenous vein bypass surgery on left ventricular volumes and ejection fraction. *American Journal of Medicine,* **54,** 290–296.

Conner, L. S., and Holt, E. (1930). The subsequent course and prognosis in coronary thrombosis. An analysis of 287 cases. *American Heart Journal,* **5,** 705–719.

Davila, J. C., and Sanmarco, M. E. (1966). An analysis of the fit of mathematical models applicable to the measurement of left ventricle volume. *American Journal of Cardiology,* **18,** 31.

Garrity, T. F. (1973). Vocational adjustment after first myocardial infarction; comparative assessment of several variables suggested in the literature. *Social Science and Medicine,* **7,** 705–717.

Judkins, M. P. (1967). Selective coronary arteriography, Part I. A percutaneous transfemoral technic. *Radiology,* **89,** 815–824.

Kjøller, E. (1976). Resumption of work after acute myocardial infarction. *Acta Medica Scandinavica,* **199,** 379–385.

Malmcrona, R., Söderholm, B., Björntorp, P., Thulesius, O., and Heyman, F. (1962). Myocardial infarction in the younger age groups. *Acta Medica Scandinavica*, **171,** 59–67.

Nitter-Hauge, S., Frøysaker, T., and Hall, K. V. (1976). Reemployment related to functional and haemodynamic changes after aortic or mitral valve replacement. *Annales chirurgiae et gynaecologiae Fenniae*, **65,** 124–131.

Shapiro, S., Weinblatt, E., and Frank, C. W. (1972). Return to work after first myocardial infarction. *Archives of Environmental Health*, **24,** 17–26.

Sharland, D. E. (1964). Ability of men to return to work after cardiac infarction. *British Medical Journal*, **2,** 718–720.

Vuopala, U. (1972). Resumption of work after myocardial infarction in Northern Finland. *Acta Medica Scandinavica*, Suppl. 530.

Weinblatt, E., Shapiro, S., Frank, C. W., and Sager, R. V. (1966). Return to work and work status following first myocardial infarction. *American Journal of Public Health*, **56,** 169–185.

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Longitudinal survey of ischaemic heart disease in randomly selected sample of older population

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A group of 215 men and 272 women aged 62 to 90 forming a randomly-selected sample of the older population was studied by cardiovascular survey methods and followed for 5 years. The 5-year mortality of 28 per cent was related to age and was higher in men. Ischaemic heart disease was the certified cause of 28 per cent of the deaths. Mortality was greater in those with systolic hypertension. Among electrocardiographic features ST depression, T inversion, and atrial fibrillation increased overall and ischaemic heart disease mortality independently of their association with age. A positive response to an angina and infarct questionnaire was poorly related to subsequent mortality.

Re-examination of 72 per cent of 5-year survivors was possible. Systolic and diastolic blood pressures were significantly lower and the frequency of electrocardiographic abnormalities, particularly left axis deviation, left ventricular hypertrophy, and ST and T wave changes, was increased.

In an earlier paper we reported (Kitchin *et al.*, 1973) on the prevalence of various manifestations of ischaemic heart disease in 487 subjects aged 62 to 90 who formed a randomly selected sample of the 27 000 older people living in a defined area of Edinburgh. Briefly this showed that 10 per cent gave a history of angina; 44 per cent had no codable electrocardiographic abnormality, 6 per cent had electrocardiographic abnormalities strongly suggestive of ischaemic heart disease, and a further 24 per cent had changes possibly caused by ischaemic heart disease. Pronounced left axis deviation was found in 8·8 per cent. Electrocardiographic evidence of ischaemic heart disease increased with age. Smoking habits, obesity, and hypertension were unrelated to manifestations of ischaemic heart disease.

This group of subjects was followed for 5 years from the initial survey and the survivors were restudied by the same methods and by the same observers. The object was to record mortality rates and the incidence of new manifestations of ischaemic heart disease in the 5-year period, and to relate these to subject characteristics at the start of the study.

Subjects and methods

The subjects were 215 men and 272 women aged 62 to 90 years. The method of sampling, including a comparison of respondents and non-respondents, has been described elsewhere (Milne *et al.*, 1971).

Standardised validated techniques were used (Kitchin *et al.*, 1973) and measures of reproducibility were obtained. The cardiovascular survey, which formed part of a larger survey, comprised the following:

(1) Rose's questionnaire in respect of angina pectoris and possible myocardial infarction (Rose and Blackburn, 1968).
(2) Twelve-lead electrocardiogram coded independently by two observers using the Minnesota code (Blackburn *et al.*, 1960). The same instrument was used throughout the study.
(3) Six-foot posteroanterior radiograph of the chest.
(4) Height, weight, skinfold thickness, and blood pressure using the London School of Hygiene instrument.
(5) Questionnaire on respiratory disease and smoking (Medical Research Council, 1965).
(6) General medical examination recorded on prepared proformata.

The χ^2 test was used to estimate the statistical significance of observed differences in the results.

Results

(1) MORTALITY AND CAUSE OF DEATH

Of the original 487 subjects, 138 died during the

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5-year period, an overall mortality of 28·3 per cent. Of these, 37 were certified as dying from myocardial infarction or ischaemic heart disease and 2 others from myocardial failure; the remaining 99 were non-cardiac deaths except for 2 from valvular heart disease. The expected death rate from national mortality statistics was 29·0 per cent (males 36%, females 24%). Table 1 shows mortality related to age and sex separating ischaemic heart disease from other deaths. In calculating death rate from ischaemic heart disease allowance has been made for the fact that those dying from non-cardiac causes were at risk of ischaemic heart disease death for 2½ years on average.

Mortality was higher in men and increased with age in both sexes. A possible relation to the following factors noted at the first examination was sought: positive response to Rose's questionnaire in respect of angina or infarction, systolic or diastolic hypertension, and specific electrocardiographic abnormalities.

Five-year mortality in those with a history of angina was 10/53 (19%) and in those without such a history it was 122/427 (29%). Deaths in those giving a history of infarction were 8/32 (25%) as compared with 125/449 (28%) in those without this history.

Table 2 shows the increased mortality in subjects with systolic or diastolic hypertension. In the case of the former, ischaemic heart disease accounts for a large proportion of the increased mortality. If we take levels of 160 and 100 as upper normal values, mortality from ischaemic heart disease was higher both for men and women with pressures over these levels.

Table 3 shows the 5-year overall and ischaemic heart disease mortality first in subjects with no codable electrocardiographic abnormality and then in groups with specific abnormalities. All types of electrocardiographic abnormality greatly increased the death rate from ischaemic heart disease, which was low (3·8%) and accounted for only 14 per cent of deaths in those with normal electrocardiograms at the start of the study. Atrial fibrillation was particularly unfavourable though numbers are small and comparison difficult. Left anterior hemiblock pattern, present in 8·8 per cent of subjects, did not significantly affect 5-year mortality.

Table 1 *5-year mortality in 487 subjects*

	No.	*Per cent mortality*	*Deaths from ischaemic heart disease as per cent of all deaths*	*Estimated death rate from ischaemia heart disease (%)*
All subjects	487	28	28	8·9
Men				
60–69	122	28	35	10·8
70+	93	47	27	15·6
All	215	36	31	12·7
Women				
60–69	137	12	6	0·8
70+	135	33	32	11·7
All	272	22	25	6·4
All 60–69	259	19	26	5·4
All 70+	228	40	30	13·2

Table 2 *5-year mortality and blood pressure*

Blood Pressure (mmHg)	*No.*	*Per cent mortality*	*Deaths from ischaemic heart disease as per cent of all deaths*	*Estimated ischaemic heart disease death rate (%)*
Systolic				
≥160	226	31	38	12·7*
≤160	261	23	19	5·6*
Diastolic				
≥100	76	38	31	13·8
≤100	411	27	28	8·1

*P < 0·005.

Since both the prevalence of electrocardiographic abnormalities and mortality increase with age, the expected mortality in the absence of the specific electrocardiographic code was calculated for separate age groups, and the resulting total expected mortality compared with the observed number of deaths in those having the electrocardiographic abnormality. This shows that ST depression, T inversion, and atrial fibrillation have an unfavourable effect independent of their association with age.

Reid *et al.* (1966) made a further classification based on the Minnesota code with the object of selecting electrocardiograms indicating probable ischaemic heart disease (I_{1-2} or VII_1) and possible ischaemic heart disease (I_3 or IV_{1-3} or V_{1-3}). These two groups showed the highest estimated death rates from ischaemic heart disease (13·2%) and overall death rates (43%) and this applied to women as much as to men and to the lower as well as to the higher age group.

CHANGES IN 5-YEAR SURVIVORS (252 subjects) Of the 349 subjects who survived 5 years, it was possible to re-examine 252 (72%). In these subjects a comparison was possible as regards response to angina questionnaire, blood pressure, and electrocardiographic coding (Tables 4, 5).

There was little overall change in frequency of positive questionnaire responses, but this conceals a considerable amount of individual change, e.g. nearly half the patients who gave a history of angina

Table 3 *5-year mortality and electrocardiogram Minnesota coding*

Code		*No.*	*Deaths*	*Deaths from ischaemic heart disease*	*Ratio observed/expected deaths (age adjusted)* *All deaths*	*Deaths from ischaemic heart disease*
No abnormality		264	63 (24%)	9 (3·4%)	—	—
I	Q/QS	37	14	4	1·24	1·03
II	Left axis deviation	46	15	6	1·07	1·30
III$_{1+2}$	LV hypertrophy	57	21	9	1·06	1·44
IV	ST depression	103	43	16	1·45‡	1·75‡
V	T inversion	138	58	20	1·59*	1·78†
VI	AV block	22	7	3	1·11	—
VII$_{1+2}$	Bundle-branch block	25	6	2	0·81	—
VIII$_3$	Atrial fibrillation	12	8	8	2·30‡	7·27†
I$_{1+2}$ or VII$_1$§		29	11	5	1·49*	4·18*
I$_3$ or IV, V$_{1-3}$¶		120	52	15		

*P < 0·005; †P < 0·010; ‡P < 0·02.

§I$_{1+2}$ or VII$_1$, probable ischaemic heart disease; ¶I$_3$ or IV, V$_{1-3}$, possible ischaemic heart disease. Classification of Reid *et al.* (1966). 'Probable' ischaemic heart disease represents major Q and QS patterns or left bundle-branch block, 'possible' minor Q abnormalities or ST-T changes.

at the first survey did not do so at the second, while none of those who gave a positive response for infarction at the first interview did so at the second.

Blood pressure fell from 151·6 ± 2·4 mmHg systolic and 79 ± 1·3 mmHg diastolic to 145·6 ± 2·5 and 77·8 ± 1·3 respectively in men, and from 163·3 ± 2·2 systolic and 88·3 ± 1·3 diastolic to 148·3 ± 2·1 and 82·6 ± 1·3 in women. The magnitude of the fall was related statistically to the height of the initial pressure.

There was an increased frequency of all electrocardiographic abnormalities at the second survey, particularly for left axis deviation, left ventricular hypertrophy, ST-T changes, bundle-branch block, and atrial fibrillation. Where criteria depend on precise voltage measurement (ventricular hypertrophy and ST-T changes) it is perhaps not surprising that some which are outside the normal range on the first examination are within it at the second, despite careful attention to standardisation.

Discussion

The observed 5-year death rate in this randomly selected sample of the older population coincides closely with that predicted from national mortality statistics (Registrar General for Scotland, 1974). This gives confidence in the unselected nature of the sample.

Table 4 *Change in 5-year survivors (252 subjects) response to angina and infarct questionnaire*

	Initial positive response	*Change after 5 years*		*Final positive response*
Angina	31/252 (12%)	−14	+16	33/252 (13%)
Infarct	14/252 (6%)	−14	+ 6	6/252 (2%)
Neither	215/252 (86%)	−18	+19	216/252 (86%)

The causes of death were found from certification data and the calculated death rates from ischaemic heart disease must, therefore, be regarded as tentative only. With this caveat, ischaemic heart disease accounted for 28 per cent of the 138 deaths in the 5-year period (31% in men and 25% in women), a figure that is rather less than expected from national statistics (37 and 36% respectively). The data confirm the sharp rising death rate with age and the higher rates in men than those in women.

An object of the longitudinal study was to examine the predictive value of patient characteristics related to ischaemic heart disease at the start of the study in respect of subsequent mortality. Positive responses to the angina and infarction questionnaire of Rose and Blackburn (1968) were unrelated to mortality in this series of subjects, though it should be noted that numbers at risk were relatively small (53 and 32). It might have been expected that those with a positive response would fare worse. However, the variability of response shown when the subjects were tested a second time must cast doubt on the reliability of the answers in older subjects, in addition to the well-known difficulty in relating chest pain to cardiac pathology in the individual case. Repeatability of the angina questionnaire has been found to be poor in both middle-aged (Rose, 1968; Zeiner-Henriksen, 1972) and elderly (Milne *et al.*, 1969) subjects.

Systolic hypertension significantly increased mortality from ischaemic heart disease. Diastolic hypertension appeared to do so also (Fig. 1), though perhaps because of the small numbers statistical

Table 5 *Changes in electrocardiographic Minnesota coding in 5-year survivors (252 subjects)*

		Initial positive finding	*Change after 5 years*	*Final positive finding*	*5-year increase in frequency (%)*
I	Q/QS	16/252 (6%)	−6 +9	19/252 (8%)	2
II	Left axis deviation	21/252 (8%)	−3 +22	40/252 (16%)	8
III$_{1+3}$	Left ventricular hypertrophy	31/252 (12%)	−9 +25	47/252 (19%)	7
IV	ST depression	39/252 (15%)	−11 +28	56/252 (22%)	7
V	T inversion	52/252 (21%)	−13 +31	70/252 (28%)	7
VI	Atrioventricular block	11/252 (4%)	−6 +7	12/252 (5%)	1
VII$_{1+2}$	Bundle branch block	16/252 (6%)	−3 +10	23/252 (9%)	3
VIII$_3$	Atrial fibrillation	12/252 (5%)	−6 +17	23/252 (9%)	4

significance was not reached. The effect of systolic hypertension on overall mortality was significant only in women. During a 14-year period in the Framingham study a raised systolic blood pressure was more strongly associated with development of ischaemic heart disease than was raised diastolic pressure (Kannel *et al.*, 1971), and the importance of systolic pressure in this association was greater with increasing age.

Ischaemic changes in the initial cardiogram, defined by Rose and Blackburn, had a strong predictive value, increasing the ischaemic heart disease death rate fourfold and the overall death rate by 50 per cent. ST and T wave abnormalities and atrial fibrillation indicated a particularly poor prognosis. Higgins *et al.* (1963), studying a younger sample of the male population aged 35 to 64, also noted an increased risk of dying, and of being recorded as dying a cardiac death, where the electrocardiogram was compatible with ischaemic heart disease, showing Minnesota Code items I, IV, and V.

We can, from the present data, record the new occurrence of electrocardiographic abnormalities in the 5-year period in the 252 examined survivors. Numerically the greatest increase is in T wave inversion (7%) and ST depression (7%) followed by left ventricular voltage increases (7%) and left axis deviation (8%). Proportionately high increases, however, also occur in atrial fibrillation (5 to 9%) and bundle-branch block (6 to 9%). These changes reflect predominantly ischaemic or conduction system disease.

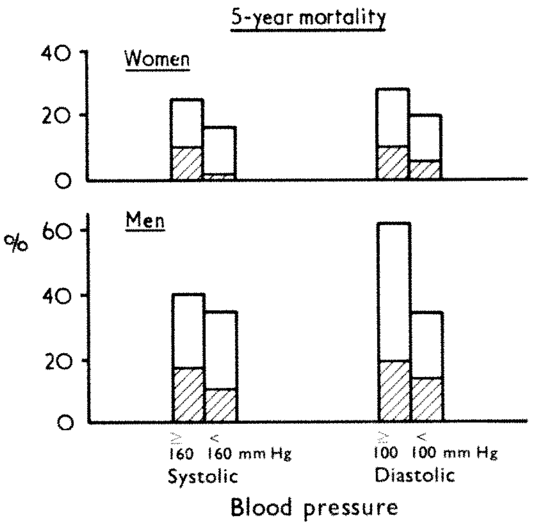

Fig. 1 *Five-year mortality (%) related to initial level of systolic and diastolic blood pressure in men and women. Cross-hatching represents deaths from ischaemic heart disease.*

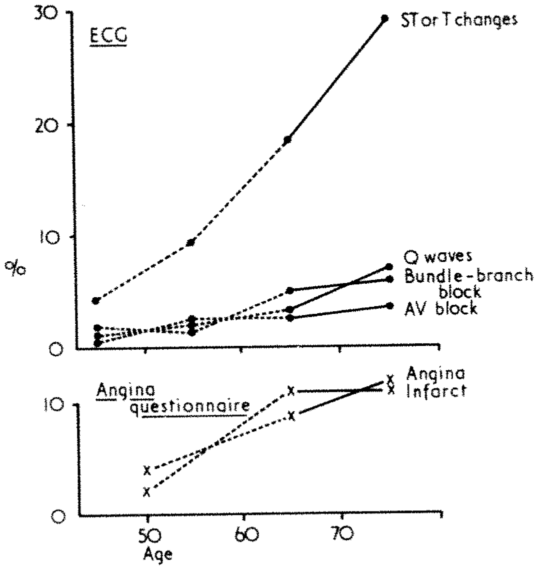

Fig. 2 *Per cent prevalence of electrocardiographic features and questionnaire responses in groups of male subjects of different ages. Solid lines—present data. Dotted lines—data of Reid* et al. *(1966).*

It is interesting to compare the increased incidence recorded in the 5-year longitudinal study with the prevalence rates in different age groups at the start of the study (Fig. 2; Kitchin *et al.*, 1973). The rates of increase with age of the prevalence of T and ST changes, Q waves, bundle-branch block, and atrioventricular block correspond closely with the observed incidence figures.

Conclusion

(1) The 5-year death rate in the older population is age- and sex-related. Both the overall death rate and deaths from ischaemic heart disease are strongly related to specific electrocardiographic abnormalities at the start of the period, ST depression, T inversion, and atrial fibrillation, but unrelated to the angina questionnaire response. Mortality from ischaemic heart disease is related to systolic blood pressure.

(2) Questionnaire responses elicited at a 5-year interval were inconsistent in many cases.

(3) In this sample, representative of the older population, the cardiographic features of ST and T wave changes, left ventricular hypertrophy, and left axis deviation each rose at a rate of approximately 1·5 per cent per annum. Conduction disturbances, atrial fibrillation, and Q wave changes developed much less frequently.

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References

Blackburn, H., Keys, A., Simonson, E., Rautaharju, P., and Punsar, S. (1960). The electrocardiogram in population studies. A classification system. *Circulation,* **21,** 1160–1175.

Higgins, I. T. T., Cochrane, A. L., and Thomas, A. J. (1963). Epidemiological studies of coronary disease. *British Journal of Preventive and Social Medicine,* **17,** 153–165.

Kannel, W. B., Gordon, T., and Schwartz, M. J. (1971). Systolic versus diastolic blood pressure and risk of coronary heart disease: the Framingham study. *American Journal of Cardiology,* **27,** 335–346.

Kitchin, A. H., Lowther, C. P., and Milne, J. S. (1973). Prevalence of clinical and electrocardiographic evidence of ischaemic heart disease in the older population. *British Heart Journal,* **35,** 946–953.

Medical Research Council Committee on the aetiology of chronic bronchitis (1965). Definition and classification of chronic bronchitis. *Lancet,* **1,** 775–779.

Milne, J. S., Hope, K., and Williamson, J. (1969). Variability in replies to a questionnaire on symptoms of physical illness. *Journal of Chronic Diseases,* **22,** 805–810.

Milne, J. S., Maule, M. M., and Williamson, J. (1971). Method of sampling in a study of older people with a comparison of respondents and non-respondents. *British Journal of Preventive and Social Medicine,* **25,** 37–41.

Registrar General for Scotland (1974). *Annual Report 1973.* H.M.S.O., Edinburgh.

Reid, D. D., Holland, W. W., Humerfelt, S., and Rose, G. A. (1966). A cardiovascular survey of British postal workers. *Lancet,* **1,** 614–618.

Rose, G. A. (1968). Variability of angina. *British Journal of Preventive and Social Medicine,* **22,** 12–15.

Rose, G. A., and Blackburn, H. (1968). *Cardiovascular Survey Methods.* World Health Organization, Geneva.

Zeiner-Henriksen, T. (1972). The repeatability at interview of symptoms of angina and possible infarction. *Journal of Chronic Diseases,* **25,** 407–414.

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P wave analysis in ischaemic heart disease
An echocardiographic, haemodynamic, and angiographic assessment[1]

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Fifty-two men with stable angina pectoris, without associated valvular heart disease or congestive failure, were studied to assess the electrocardiographic P wave abnormalities and their relation to left atrial size, pressure, and left ventricular function. Their mean age was 52 years. Duration of P waves in leads II, III, and aVF and the P terminal force in V1 were examined. Echocardiograms were obtained to assess left atrial size and left atrial-aortic ratio. These measurements were also made in 33 normal subjects. Mean pulmonary artery wedge pressure at rest and exercise, left ventricular asynergy, ejection fraction, and severity of coronary artery disease were determined in all 52 patients.

P terminal force more negative than –0·02 mm s was noted in 69 per cent of coronary artery disease patients but in none of the normal subjects. P terminal force correlated with exercise pulmonary artery mean wedge pressure but not with left atrial size. P wave duration in lead II did not correlate with pulmonary artery mean wedge pressure or left atrial size. P terminal force correlated with left ventricular contraction abnormality but not with ejection fraction or number of vessels diseased. It is suggested that chronic intermittent increases in left atrial pressure in association with angina pectoris result in left atrial hypertrophy which is responsible for the increased magnitude of P terminal force in V1 in patients with ischaemic heart disease.

Morphological changes in the P wave of the electrocardiogram have been seen in valvular heart disease (Morris *et al.*, 1964; Gooch *et al.*, 1966; Kasser and Kennedy, 1969; Rubler *et al.*, 1976), hypertension (Ross, 1963; Tarazi *et al.*, 1966), heart failure (Wood and Selzer, 1939; Sutnick and Soloff, 1962; Romhilt and Scott, 1972), acute myocardial infarction (Master, 1933; Grossman and Delman, 1969; Heikkilä and Luomanmäki, 1970; Chandraratna and Hodges, 1973), and ischaemic heart disease (Bethell and Nixon, 1972; Rios *et al.*, 1974). P wave abnormalities have been correlated with atrial hypertrophy caused by pressure overload and atrial enlargement resulting from volume overload. Abnormal P waves may also result from atrial conduction defects.

In 1964 Morris and his colleagues noted that the P terminal force in lead V1 correlated with left atrial pressure or volume overload in patients with valvular heart disease. They proposed that a P terminal force with an area of negative value exceeding –0·03 mm s was usually diagnostic of left atrial involvement (Morris *et al.*, 1964). Other commonly used electrocardiographic criteria for left atrial enlargement consist of a P wave duration of 0·12 s or more in the limb leads (Massie and Walsh, 1960).

Previous studies in stable angina pectoris have revealed P wave abnormalities in 18 to 51 per cent of patients. The abnormal P waves suggested the presence of left atrial enlargement but left atrial size was not determined and the patients had not been studied by coronary arteriography (Bethell and Nixon, 1972; Rios *et al.*, 1974).

This study was undertaken to evaluate the P wave abnormalities in patients with stable angina pectoris who have had haemodynamic and angiographic studies as well as a determination of left atrial size by echocardiography.

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Methods

A total of 52 patients with stable angina pectoris who had entered the Palo Alto Veterans Administration Hospital between 1972 and 1975 were studied. All were men and their mean age was 52 years (range 34 to 66). All were considered suitable for saphenous vein bypass graft surgery on the basis of clinical studies and the presence of significant obstructive coronary arterial disease. Significant coronary lesions were judged to be present when arteriography showed a 50 per cent or more reduction in diameter of the lumen.

Patients with valvular heart disease, congestive heart failure, and frequent cardiac arrhythmias were excluded. Of the 52 patients, 24 (46%) had electrocardiographic evidence of a prior myocardial infarction and 9 (17%) had hypertension (systolic pressure exceeding 150 mm and diastolic pressure exceeding 90 mm). Two patients (4%) had electrocardiographic evidence of left ventricular hypertrophy.

All patients were studied by cardiac catheterisation, coronary arteriography, and left ventriculography. Cardiac outputs by the Fick method were obtained and pulmonary artery wedge pressures were recorded at rest and during moderate supine cycle-ergometry exercise. Arteriography was performed using the Judkins technique. Left ventricular contraction abnormalities were identified and ejection fractions were calculated by determination of the major and minor axis of the left ventricular chamber at end systole and end diastole. Echocardiograms were recorded using a strip chart recorder (36 patients) or by photographs taken from a Polaroid camera (16 patients). Left atrial diameter was determined at end systole and aortic diameter was measured during end diastole. A left atrial-aortic ratio equal to or greater than 1·2 or a left atrial dimension equal to or greater than 4·2 cm were considered to indicate left atrial enlargement (Brown *et al.,* 1974). Echocardiograms and electrocardiograms were recorded on the same day.

All patients had resting standard 12-lead electrocardiograms recorded at standard paper speed. The electrocardiogram was recorded within 24 hours of the haemodynamic study. None of the patients had chest pain while the electrocardiogram was recorded. P wave abnormalities were not changed in serial electrocardiograph tracings. P wave amplitude and duration were determined by a single observer using a hand lens and callipers. The P terminal force in mm s was calculated from the terminal negative deflection of the P wave in lead V1 using the method of Morris *et al.* (1964) as shown in Fig. 1.

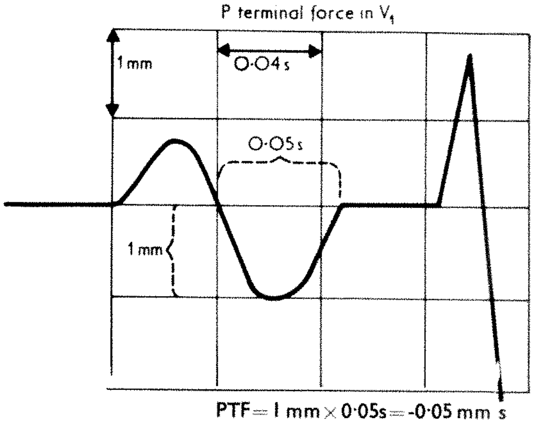

Fig. 1 *Calculation of P terminal force (PTF) from terminal deflection of P wave in V1 is shown. Duration in seconds is multiplied by the maximum negative amplitude in millimetres to obtain P terminal force in mm s.*

Control data were obtained from 33 normal subjects with a mean age of 37 years (21 to 59). Electrocardiograms and echocardiograms were evaluated by the same methods used in the study group. Haemodynamic and angiocardiographic studies were not performed in the control group.

The data obtained by the above studies were analysed to determine:

(1) The prevalence and nature of P wave abnormalities in patients with coronary disease compared with normal controls.

(2) The correlation of P wave abnormalities with: (a) left atrial diameter determined by echocardiography; (b) pulmonary artery wedge pressure at rest and during exercise; (c) left ventricular contraction pattern and ejection fraction; (d) number of coronary arteries with significant obstructive disease.

Table 1 *P wave characteristics in patients with coronary artery disease and normal subjects*

P wave characteristics	*Coronary artery disease (n = 52)*		*Normal subjects (n = 33)*	
	No.	%	*No.*	%
(1) P wave duration limb leads				
(a) < 0·11 s	23	44	29	88
(b) ≥ 0·11 but < 0·12 s	11	21	4	12
(c) ≥ 0·12 s	18	35	0	0
(2) PTF–V1 mm s				
(a) Equal to or less negative than –0·02	16	31	33	100
(b) More negative than –0·02	36	69	0	0

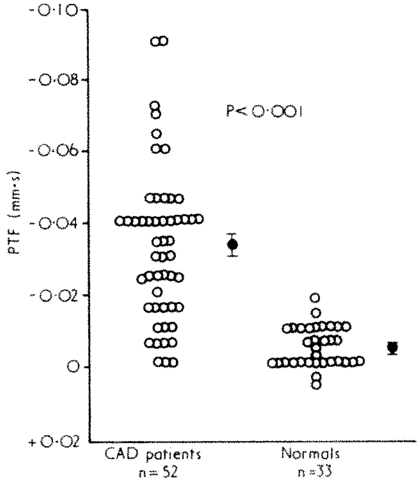

Fig. 2 *Range of P terminal force in patients with ischaemic heart disease and in normal subjects. The mean value and ±1 standard error of the mean are shown. PTF=P terminal force.*

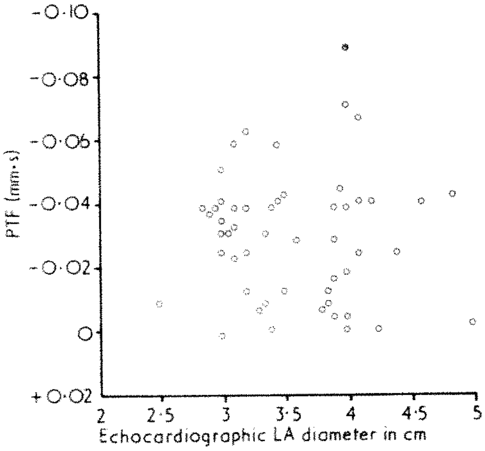

Fig. 3 *Relation between P terminal force (PTF) and echocardiographic left atrial diameter in 52 patients with ischaemic heart disease. There was no significant correlation by linear regression between these variables. A poor correlation was also noted when P terminal force (PTF) was compared with echocardiographic left atrial aortic ratio (LA/Ao) ratio.*

Results

Eighteen of 52 patients (35%) had a P wave duration in the limb leads equal to or greater than 0·12 s. None of the normal subjects had a P wave duration of greater than 0·11 s (Table 1).

Of the 52 patients, 36 (69%) had a P terminal force more negative than –0·02 mm s but none of the normal subjects exceeded that value. The difference was significant (–0·0331 ±0·0029 versus –0·0045 ±0·0008) with a P value of <0·001 (Fig. 2).

P wave duration in extremity leads and P terminal force correlated poorly with left atrial aortic ratio or left atrial diameter (Fig. 3). Of all 52 patients, 24 (46%) had evidence of increased left atrial diameter; 16 of 36 patients (44%) with abnormal P terminal force values had evidence of increased left atrial diameter. None of the normal subjects had abnormal left atrial size.

P wave duration in the limb leads did not correlate with pulmonary artery mean wedge pressure at rest or during exercise.

P terminal force showed a significant correlation with pulmonary artery wedge pressure during exercise with a P value of <0·001 and an r value of 0·54 (Fig. 4). The correlation with resting pulmonary artery wedge pressure was not significant.

Twenty-two patients who had a rise of pulmonary artery wedge pressure of greater than 10 mmHg during exercise had a more negative P terminal force (0·0475 ±0·0043) than 30 patients who had a lesser rise in pulmonary artery wedge pressure (–0·0219 ±0·0026). The difference was significant with a P value <0·001. The data are summarised in Fig. 5.

Patients with angiocardiographic evidence of abnormalities in left ventricular contraction had P terminal force values that were more abnormal (–0·0376 ±0·0035) than patients with normal left ventricular contraction (–0·0249 ±0·0048). The difference was significant with a P value of <0·05 (Fig. 6).

No correlation was noted between P terminal force values and the number of significantly ob-

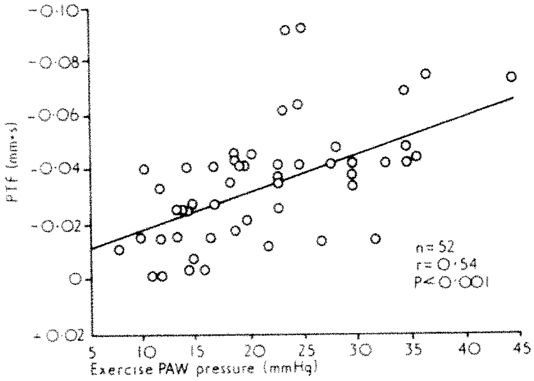

Fig. 4 *Linear regression of P terminal force (PTF) versus pulmonary artery wedge (PAW) pressure during exercise in patients with ischaemic heart disease.*

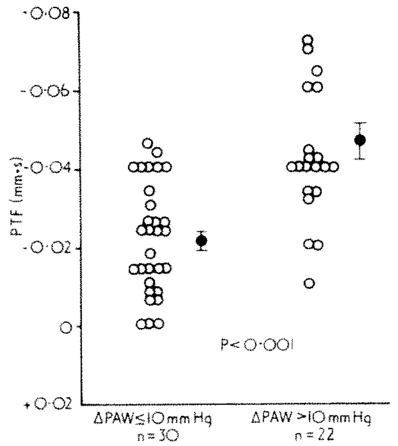

Fig. 5 *Values of P terminal force (PTF) in two groups of patients with ischaemic heart disease. The group on the left had a rise in pulmonary arterial wedge pressure with exercise equal to or less than 10 mmHg and the group on the right raised pulmonary artery wedge pressure with exercise by more than 10 mmHg. The closed circles indicate the means and the brackets ±1 standard error of the mean.*

Table 2 *Coronary artery disease and left ventricular ejection fraction in patients with normal or abnormal P terminal force*

	P terminal force equal to or less neg than −0·02 mm s		*P terminal force more neg than −0·02 mm s*
No. of vessels with obstruction	1·88 ±0·20 (n = 16)	NS	2·11 ±0·12 (n = 36)
Ejection fraction (%)	76·5 ±3·7 (n = 16)	NS	68 ±4·0 (n = 36)

structructed coronary arteries or with left ventricular ejection fraction (Table 2).

There was no correlation between left atrial size and pulmonary artery wedge pressure at rest or during exercise.

Discussion

P wave abnormalities in ischaemic heart disease have been studied in acute myocardial infarction (Master, 1933; Grossman and Delman, 1969; Heikkilä and Luomanmäki, 1970; Chandraratna and Hodges, 1973) but few studies have been done in patients with stable angina pectoris. Bethell and Nixon (1972) noted that in 152 patients with angina the incidence of a P terminal force more negative than −0·02 s was 18 per cent compared with an incidence of 0·5 per cent in 206 normal subjects. Rios *et al.* (1974) noted P wave abnormalities compatible with left atrial abnormalities in 51 per cent of 84 patients with ischaemic heart disease.

In the present study the higher incidence of P terminal force abnormalities (69%) is probably related to the presence of more severe disease in the study population. The difference cannot be explained by the incidence of previous myocardial infarction since patients with previous infarction had the same incidence of P terminal force abnormalities (71·4%) as patients without earlier infarction (70·8%). However, the incidence of abnormal P terminal force in this study would be significantly lower (46% or 24/52) if Morris's criteria were used for abnormal P terminal force.

Morris and his colleagues (1964) evaluated P wave abnormalities in valvular heart disease and suggested that a P terminal force equal to or less negative than −0·03 mm s could be considered normal. Bethell and Nixon, however, suggested that a P terminal force of −0·02 mm s should be the limit of normality. The present study supports this latter view.

The duration of the P wave in extremity leads is less useful than the P terminal force as a sign of left atrial pressure overload. P wave duration did not correlate with the rise in pulmonary artery

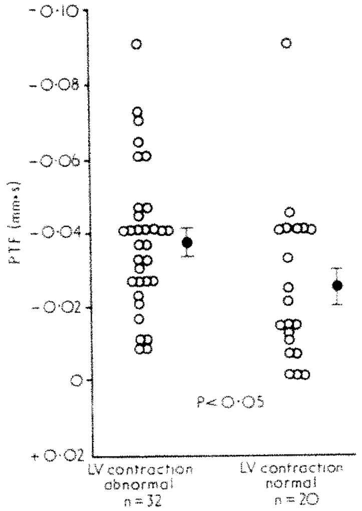

Fig. 6 *Values of P terminal force (PTF) in two groups of patients with ischaemic heart disease. The group on the left had left ventricular (LV) contraction abnormalities on angiography and the group on the right had normal left ventricular contractions. The closed circles indicate the means and the brackets ±1 standard error of the mean.*

wedge pressure during exercise whereas the P terminal force did.

By echocardiographic criteria an increase in left atrial dimension was noted in 44 per cent of patients. Left atrial size, however, correlated poorly with the duration of the P wave in the ECG limb leads and the P terminal force. The P terminal force correlated significantly with pulmonary artery wedge pressure during exercise. Patients who had a rise in pulmonary artery wedge pressure of >10 mmHg had more abnormal P terminal force values than patients who had a lesser rise in pulmonary artery mean wedge pressure. Abnormal P terminal force values also correlated with abnormalities in left ventricular function. These observations suggest that abnormal P terminal force values in angina pectoris are the result of pressure overload and not of an increase in left atrial size alone. It is now well known that spontaneous or induced angina is frequently associated with a rise in left ventricular end diastolic pressure (Kasparian and Wiener, 1968). In patients with chronic angina repeated elevations of diastolic pressure could result in left atrial hypertrophy which may not be accompanied by an increase in left atrial volume. Anatomical studies correlating left atrial wall thickness and left atrial volume with P wave abnormalities in ischaemic heart disease are needed to investigate this hypothesis. The data relating P wave abnormalities to left atrial anatomy available at present are not sufficient to answer this question (Bachmann, 1941; Pirani and Langendorf, 1949; Mazzoleni *et al.*, 1964; Kasser and Kennedy, 1969; Romhilt *et al.*, 1972).

Of the 52 patients, 4 had a P terminal force more negative than -0·03 mm s with a normal pulmonary artery mean wedge pressure during exercise and normal left atrial dimensions. Factors other than pressure overload or atrial dilatation are probably responsible for the P wave abnormalities in those patients. Saunders *et al.* (1967) have noted that P wave abnormalities may be present in patients with normal left atrial dimensions. Atrial conduction abnormalities involving Bachmann's bundle may result in P wave abnormalities (Bachmann, 1941). It is, therefore, likely that some P wave abnormalities in ischaemic heart disease may be the result of atrial conduction defects resulting from atrial infarction or ischaemic injury as well as infiltrative or inflammatory disease.

P wave abnormalities may be present in patients with systemic hypertension (Ross, 1963; Tarazi *et al.*, 1966). In the present study 9 patients had hypertension and abnormal P terminal force values were present in 7 of these patients. The incidence was only slightly greater than that observed in patients without hypertension; hence hypertension could not explain the high incidence of P terminal force values observed in the present study.

In conclusion, this study has shown that patients with stable angina pectoris frequently have abnormal P waves in lead V1 consisting of a P terminal force more negative than -0·02 mm s. This abnormality can be correlated with a rise in left ventricular filling pressure during exercise and abnormal left ventricular function, but not with left atrial diameter. An abnormal P terminal force in lead V1 is more commonly observed than an increased P wave duration. It is suggested that the P wave abnormalities in most patients with angina pectoris are the result of intermittent rises of left atrial pressure occurring during episodes of left ventricular ischaemia. Left atrial hypertrophy rather than left atrial dilatation appears to be the more likely anatomical cause of the P wave abnormalities; this possibility requires investigation by anatomical studies.

References

Bachmann, G. (1941). The significance of splitting of the P wave in the electrocardiogram. *Annals of Internal Medicine*, **14**, 1702–1709.

Bethell, H. J. N., and Nixon, P. G. F. (1972). P wave of electrocardiogram in early ischaemic heart disease. *British Heart Journal*, **34**, 1170–1175.

Brown, O. R., Harrison, D. C., and Popp, R. L. (1974). An improved method for echographic detection of left atrial enlargement. *Circulation*, **50**, 58–64.

Chandraratna, P. A. N., and Hodges, M. (1973). Electrocardiographic evidence of left atrial hypertension in acute myocardial infarction. *Circulation*, **47**, 493–498.

Gooch, A., Calatayud, J. B., Rogers, J. B., and Gorman, P. A. (1966). Analysis of P wave in severe aortic stenosis. *Diseases of the Chest*, **49**, 459–463.

Grossman, J. I., and Delman, A. J. (1969). Serial P wave changes in acute myocardial infarction. *American Heart Journal*, **77**, 336–341.

Heikkilä, J., and Luomanmäki, K. (1970). Value of serial P wave changes in indicating left heart failure in myocardial infarction. *British Heart Journal*, **32**, 510–517.

Kasparian, H., and Wiener, L. (1968). Left ventricular compliance and volume changes in coronary heart disease. *Circulation*, **38**, 240.

Kasser, I., and Kennedy, J. W. (1969). The relationship of increased left atrial volume and pressure to abnormal P waves on the electrocardiogram. *Circulation*, **39**, 339–343.

Massie, E., and Walsh, T. J. (1960). *Clinical Vectorcardiography and Electrocardiography.* Yearbook Medical Publishers, Chicago.

Master, A. M. (1933). P wave changes in acute coronary artery occlusion. *American Heart Journal*, **8**, 462–470.

Mazzoleni, A., Wolff, R., Wolff, L., and Reiner, L. (1964). Correlation between component cardiac weights and electrographic patterns in 185 cases. *Circulation*, **30**, 808–829.

Morris, J. J., Estes, E. H., Whalen, R. E., Thompson, H. K., and McIntosh, H. D. (1964). P wave analysis in valvular heart disease. *Circulation*, **29**, 242–252.

Pirani, C. L., and Langendorf, R. (1949). Pathology of the cardiac atria. An anatomic-electrocardiographic correlation based on a study of 85 human hearts (abstract). *American Heart Journal,* **37,** 663.

Rios, J. C., Schatz, J., and Meshel, J. C. (1974). P wave analysis in coronary artery disease: an electrocardiographic-angiographic and hemodynamic correlation. *Chest,* **66,** 146–150.

Romhilt, D. W., Bove, K. E., Conradi, S., and Scott, R. C. (1972). Morphologic significance of left atrial involvement. *American Heart Journal,* **83,** 322–327.

Romhilt, D. W., and Scott, R. C. (1972). Left atrial involvement in acute pulmonary edema. *American Heart Journal,* **83,** 328–331.

Ross, G. (1963). Effect of hypertension on the P wave of the electrocardiogram. *British Heart Journal,* **25,** 460–464.

Rubler, S., Shah, N. N., and Moallem, A. (1976). Comparison of left atrial size and pulmonary capillary pressure with P wave of electrocardiogram. *American Heart Journal,* **92,** 73–78.

Saunders, J. L., Calatayud, J. B., Schulz, K. J., Maranhao, V., Gooch, A. S., and Goldberg, H. (1967). Evaluation of ECG criteria for P wave abnormalities. *American Heart Journal,* **74,** 757–765.

Sutnick, A. I., and Soloff, L. A. (1962). Posterior rotation of the atrial vector. An electrocardiographic sign of left ventricular failure. *Circulation,* **26,** 913–916.

Tarazi, R. C., Miller, A., Frohlich, E. D., and Dustan, H. P. (1966). Electrocardiographic changes reflecting left atrial abnormality in hypertension. *Circulation,* **34,** 818–822.

Wood, P., and Selzer, A. (1939). A new sign of left ventricular failure. *British Heart Journal,* **1,** 81–85.

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Early diastolic murmurs in end-stage renal failure

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An early diastolic murmur thought to indicate functional aortic regurgitation was heard in 7 of 74 consecutive patients with end-stage renal failure assessed for chronic intermittent haemodialysis and transplantation. In all 7 cases the murmur was transient and related to episodes of hypertension and fluid overload and disappeared on correction of these factors. In a further 2 patients aortic regurgitation resulted from a structural abnormality of the aortic valve. Thus, an early diastolic murmur is not uncommon in this situation and does not necessarily indicate organic aortic valve disease which might preclude selection for haemodialysis and transplantation.

The causes of aortic regurgitation are many and are well reviewed by Runco and Booth (1963). Functional aortic regurgitation has been described as a rare occurrence in anaemia (Hunter, 1946) and congestive cardiac failure (McKusick, 1958). In hypertension the prevalence of functional aortic regurgitation has been reported as varying from 2 per cent (Paullin *et al.*, 1927) to 9 per cent (Barlow and Kincaid Smith, 1960).

In end-stage renal failure, anaemia is invariable, hypertension is usual, and congestive cardiac failure not uncommon. There might, therefore, be expected to be a high incidence of functional aortic regurgitation in such patients, leading to errors in management, unless this is recognised as such (Matalon *et al.*, 1971). We examined and followed up all patients referred to a Regional Renal Unit for assessment for haemodialysis over a two-year period to assess the incidence of aortic diastolic murmurs.

Results

The 74 patients studied were all those assessed as to their suitability for long-term haemodialysis and transplantation on account of end-stage renal failure. In the course of the study 9 were noted by at least 2 observers to have an early diastolic murmur. Two of these clearly had organic aortic valve disease: 1 had been investigated by cardiac catheterisation and a diagnosis of congenital aortic regurgitation made; the other developed aortic regurgitation in the course of a staphylococcal septicaemia and died, necropsy revealing bacterial endocarditis involving the aortic valve. In the other 7 patients (see Table for details) the murmur was transient, suggesting that this was caused by functional aortic regurgitation.

A representative history is that of case 4, a 24-year-old man first seen in 1967 complaining of headache. Physical examination showed a blood pressure of 220/130 mmHg, left ventricular hypertrophy, and grade 4 hypertensive retinopathy. He was treated with methyldopa 1 g t.d.s. Twelve months later he was admitted to the renal unit with increasing shortness of breath. He was then found to have a blood pressure of 200/110 mmHg and grade 2 hypertensive retinopathy. Jugular venous pressure was raised 4 cm and there was mild peripheral oedema. On auscultation of the heart there was a soft systolic ejection murmur, a loud aortic valve closure sound, and an early diastolic murmur. Crepitations were heard at both lung bases. The electrocardiogram showed left ventricular hypertrophy, and the chest radiograph showed cardiomegaly and pulmonary oedema. Blood urea was 500 mg/100 ml (83 mmol/l). Peritoneal dialysis was performed and over the next three days he improved considerably: blood pressure fell to 170/100 mmHg, pulmonary and peripheral oedema cleared, and he lost 5 kg in weight; the early diastolic murmur disappeared. He was started on intermittent haemodialysis and methyldopa was continued. He remained well until 6 months later when he again became breathless. He was 5 kg above his estimated ideal weight and his blood pressure was 210/110 mmHg.

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Table *Details of patients with end-stage chronic renal failure found to have an early diastolic murmur*

Case No.	*Age (y)*	*Sex*	*Diagnosis*	*Hb (g/dl)*	*Lowest recorded BP when murmur present (mmHg)*	*Highest recorded BP when no murmur present (mmHg)*	*Evidence of fluid overload*
1	27	M	GN	6	160/95	220/140	PD
2	24	M	GN	7	176/110	270/170	P
3	36	F	GN	6	180/120	200/130	P
4	28	F	GN	5	160/90	210/140	PD
5	40	M	VUR	6	160/100	210/115	PD
6	16	F	VUR	6	140/80	160/90	PD
7	23	M	H/T after pregnancy toxaemia	6	170/110	200/150	PD

GN, glomerulonephritis; VUR, vesico-ureteric reflux; H/T, hypertension; P, pulmonary oedema; D, dependent oedema

He had peripheral and pulmonary oedema and again an early diastolic murmur was heard. His dialysis regimen was adjusted and his sodium and water intake restricted. He improved and the early diastolic murmur disappeared. Over the next 2 years he was admitted on 3 occasions, with shortness of breath and clinical and radiological evidence of pulmonary oedema. On each occasion he was well above his estimated ideal weight and a transient early diastolic murmur was heard; his blood pressure on these 3 occasions was 160/90, 210/110, and 180/95 mmHg. Since then he has had a successful renal transplant.

Details of the other patients can be seen in the Table. All were anaemic. All presented with symptoms suggesting fluid overload and were found to have dependent oedema and/or cardiac enlargement with pulmonary oedema on chest *x*-ray examination. Six were hypertensive at the time the murmur was heard, though in every case a higher blood pressure had been recorded at other times without a murmur being audible. In all cases the murmur disappeared after dialysis. Three patients had forearm arteriovenous shunts when the murmur was first heard (cases 1, 2, and 3). No patient had a history of rheumatic fever. All had negative serological tests for syphilis and sterile blood cultures. Cases 5 and 6 had been hypercalcaemic in the past; band keratopathy and ear drum calcification were present in cases 1, 2, and 3, and case 5 had severe peripheral vascular calcification.

Three patients have had successful transplants and 4 have died, case 3 from myocardial infarction, cases 5 and 6 from uraemia, and case 7 from septicaemia. Necropsy in cases 3 and 5 showed normal aortic valves.

Discussion

The early diastolic murmur in these patients was thought to be the result of aortic regurgitation and to be functional in 7 of the 9. Pulmonary regurgitation was a possible alternative but was unlikely in the absence of any evidence of pulmonary hypertension.

All, except one, of the patients were hypertensive, though each had been seen at other times with a higher blood pressure but no murmur. This confirms the observation of Puchner *et al.* (1960) that functional aortic regurgitation in hypertension is not simply related to the height of the blood pressure. The incidence of functional aortic regurgitation in our patients (9·5%) is higher than in most reported series of hypertensive patients (Paullin *et al.*, 1927; Garvin, 1940; Puchner *et al.*, 1960) though Barlow and Kincaid Smith (1960) found a 9 per cent incidence in their series of 100 patients at the Postgraduate Medical School of London. This also suggests that factors other than hypertension alone were responsible for the aortic regurgitation.

Fluid overload was present in all the patients and the murmur invariably disappeared when this was corrected. However, as commonly occurs in chronic renal failure, dialysis corrected the hypertension and fluid overload simultaneously; it is, therefore, difficult to judge the relative importance of these two factors. It seems likely that fluid overload was the major determinant, since symptoms of cardiac failure with shortness of breath and/or oedema were invariable presenting features and though hypertension was present it was not as severe as on previous occasions when there had been no aortic regurgitation. Anaemia is unlikely to have been an important factor since the murmurs disappeared without a rise in haemoglobin level. It may, however, have made it possible to detect some murmurs that would otherwise have been inaudible, as there is evidence that a low blood viscosity increases the intensity of murmurs (Garb, 1944).

We did not consider the presence of peripheral vascular calcification to be relevant since this is a common finding in end-stage renal failure and no aortic valve calcification was visible on chest *x*-ray films. It is interesting, however, that no fewer than

3 patients had band keratopathy and ear-drum calcification, which are much less common complications of renal failure.

We conclude that there is a relatively high incidence of aortic regurgitation in patients with end-stage renal failure; this is usually functional, occurring in the presence of fluid overload and hypertension, and is reversible by dialysis.

We thank Professor H. A. Lee for permission to include patients under his care, Dr. J. Burston for the necropsy examinations, and Dr. D. W. Barritt for helpful advice.

References

Barlow, J., and Kincaid Smith, P. (1960). Auscultatory findings in hypertension. *British Heart Journal,* **22,** 505–514.

Garb, S. (1944). The relationship of blood viscosity to the intensity of heart murmurs. *American Heart Journal,* **28,** 568–573.

Garvin, C. F. (1940). Functional aortic insufficiency. *Annals of Internal Medicine,* **13,** 1799–1804.

Hunter, A. (1946). The heart in anaemia. *Quarterly Journal of Medicine,* **15,** 107–124.

McKusick, V. A. (1958). *Cardiovascular Sound in Health and Disease.* Williams and Wilkins, Baltimore.

Matalon, R., Moussalli, A. R. J., Nidus, B. D., Katz, L. A., and Eisinger, R. P. (1971). Functional aortic insufficiency—a feature of renal failure. *New England Journal of Medicine,* **285,** 1522–1523.

Paullin, J. E., Bowcock, H. M., and Wood, R. H. (1927). Complications of hypertension. *American Heart Journal,* **2,** 613–617.

Puchner, T. C., Huston, J. H., and Hellmuth, G. A. (1960). Aortic valve insufficiency in arterial hypertension. *American Journal of Cardiology,* **5,** 758–760.

Runco, V., and Booth, R. W. (1963). Basal diastolic murmurs. *American Heart Journal,* **65,** 697–708.

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Myocardial infarction after aortocoronary saphenous vein bypass

Vectorcardiographic study[1]

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Vectorcardiograms and scalar electrocardiograms were recorded in 30 patients before and after aortocoronary saphenous vein bypass surgery to determine whether vectorcardiograms are helpful in making the diagnosis of perioperative transmural infarction. The vectorcardiogram indicated inferior infarction in 2 cases and anterior infarction in 1 case when the diagnosis was not apparent on the electrocardiogram. In the solitary case of anterior infarction diagnosed by the electrocardiogram, anterior infarction was already present on the preoperative vectorcardiogram.

The study indicates that the recording of vectorcardiograms before and after aortocoronary bypass surgery facilitates the diagnosis of perioperative anterior and inferior infarction and may reveal perioperative infarction about a previously infarcted area.

Since aortocoronary bypass by saphenous vein graft was first reported (Favaloro, 1968), the operation has gained widespread acceptance as a means of relieving angina pectoris in a large majority of patients. However, the procedure is frequently associated with electrocardiographic features of myocardial infarction. The limitations of the electrocardiogram in diagnosing infarction are well known and it has been frequently shown that the vectorcardiogram can diagnose infarction which is not apparent on the electrocardiogram (Hugenholtz *et al.*, 1961; Wolff *et al.*, 1961; Simonson *et al.*, 1966; Gunnar *et al.*, 1967). It was the aim of this investigation to determine whether use of the vectorcardiogram in addition to the electrocardiogram is helpful in making the diagnosis of infarction attributable to aortocoronary bypass surgery.

Subjects and methods

Thirty patients aged between 36 and 66 years who had been admitted to the Royal Victoria Hospital, Montreal, for aortocoronary saphenous vein bypass were examined. Patients who underwent additional procedures were not included. Record was made of previous episodes of myocardial infarction. An electrocardiogram and vectorcardiogram were recorded on each patient during the 72 hours before operation, and from 7 to 10 days after operation; corresponding electrocardiograms and vectorcardiograms were recorded within one hour of one another. A direct-writing Sanborn electrocardiograph was used to record the standard 12-lead electrocardiogram. A Sanborn Model 185-100 vectorcardiograph was employed and the vectorcardiograms were recorded by a Polaroid camera set at f8 and 0·5 s, using black and white Polaroid film, type 107. The vectorcardiograms were recorded with the patient in the recumbent position; the Frank lead system was employed (Frank, 1956).

Conventional electrocardiographic criteria (Perloff, 1964; Schrank *et al.*, 1974) and vectorcardiographic criteria (Chou and Helm, 1967; Gunnar *et al.*, 1967; McConahay *et al.*, 1970; Starr *et al.*, 1974) of known value in the diagnosis of transmural myocardial infarction were employed. T loop changes were not considered diagnostic of infarction and were examined separately. Conduction disturbances were also sought.

In evaluating the incidence of perioperative

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transmural infarction within various subgroups, cases with electrocardiographic, vectorcardiographic, and postmortem evidence of infarction were considered together since necropsy of hearts with infarction not associated with operation has shown that the diagnostic accuracy of the vectorcardiogram and electrocardiogram together exceeds either method alone (Burch *et al.*, 1958).

The vectorcardiograms were analysed to detect any change in direction of the maximum projection of the T vector in the frontal, horizontal, and right sagittal planes. When the spatial vector is almost perpendicular to the projection being examined very small changes in the direction of the vector can cause great alterations in its projection. Therefore, changes in direction of the maximum T vector were considered evidence of a change in the T loop only when these were more than 20° in at least two planes.

Results

QRS CHANGES

Before bypass surgery 15 patients had electrocardiographic evidence of infarction (Table 1). The vectorcardiogram also showed evidence of infarction in these cases, but in 6 cases the sites of infarction differed. In addition, the vectorcardiogram indicated anterior infarction in 2 cases, one of which was supported by clinical history, though there was no evidence of infarction on the scalar electrocardiogram, and suggested posterior infarction in another when there was a normal electrocardiogram and no apparent history of infarction. Twelve patients had neither electrocardiographic nor vectorcardiographic evidence of infarction before operation, though 2 gave histories of infarction.

Table 1 *Transmural infarction before and after aortocoronary bypass surgery*

Case No.	*History of previous infarction*	*Preoperative*		*Postoperative change*	
		ECG	*VCG*	*ECG*	*VCG*
1	Yes	A	A, L	—	—
2	Yes	A, L, I	A, I	—	—
3	Yes	A, I	A, I	—	—
4	Yes	I	I	—	—
5	No	—	—	—	—
6	Yes	A	A	(Died)	(Died)
7	Yes	—	—	—	—
8	Yes	I	I	—	—
9	Yes	I	I	—	A
10	Yes	I	I, A	A	—
11	No	—	—	—	—
12	Yes	I	I, P	—	—
13	Yes	—	P	—	I
14	No	—	—	—	—
15	Yes	—	—	—	—
16	No	—	A	—	—
17	Yes	—	—	—	I
18	Yes	A	A, I	—	—
19	No	—	—	—	—
20	No	—	—	—	—
21	Yes	P	P	—	—
22	No	—	—	—	—
23	No	—	—	—	—
24	Yes	I	I	—	—
25	Yes	—	A	—	—
26	No	—	—	—	—
27	Yes	I	I	—	—
28	Yes	I	I	—	—
29	Yes	A	A, I	—	—
30	No	—	—	—	—

ECG, electrocardiogram; VCG, vectorcardiogram; A, anterior; L, lateral; P, posterior; I, inferior.

Only one patient died during the period of the study (operative mortality 3%). This death occurred 36 hours after operation and necropsy showed extensive recent inferior myocardial infarction; there was clinical, electrocardiographic and vectorcardiographic evidence of previous anterior infarction.

Four other patients showed electrocardiographic features of perioperative infarction (13%) but there was no agreement between the vectorcardiogram and electrocardiogram in indicating infarction. In 3 patients infarction was only apparent on the vectorcardiogram: 2 had an inferior and 1 an anterior infarct. The electrocardiogram showed anterior infarction in 1 patient in whom the vectorcardiogram, but not the electrocardiogram, had already shown preoperative anterior infarction (Table 1).

Three patients without apparent infarction developed left posterior hemiblock after operation (10%) and another left anterior hemiblock (3%); no patient developed bundle-branch block.

When vectorcardiograms were examined before and after operation, alterations in the T loop were noted in 19 out of 29 cases (one of whom died) (Table 2). Those with a history of previous infarction were more susceptible to T loop changes ($P < 0{\cdot}01$).

Discussion

Determination of the incidence of myocardial infarction caused by aortocoronary saphenous vein bypass surgery is important for two reasons: (1) because of the complications of myocardial infarction, and (2) because the relief of angina may be the result of perioperative infarction of ischaemic myocardium (Friedewald *et al.*, 1973; Schatz, 1973).

The cause of relief of angina pectoris in individual patients is difficult to assess; it has been shown that sham operations may relieve angina in 95 per cent of cases (Battezzati *et al.*, 1959) and relief of pain may be the result of interruption of afferent nerve

Table 2 *Change in direction of maximum projection of T vector*

Case No.	*Change in direction of maximum projection of T vector (degrees)*		
	Horizontal	*Frontal*	*Right sagittal*
1	0	80	40
2	0	100	5
3	95	80	120
4	25	5	40
5	15	10	5
6	—	—	—
7	35	40	95
8	0	30	10
9	25	55	50
10	0	25	70
11	25	5	0
12	30	10	85
13	175	50	140
14	75	25	30
15	90	30	40
16	10	20	0
17	60	25	20
18	25	10	25
19	35	30	40
20	0	20	25
21	100	5	100
22	25	5	10
23	55	15	20
24	35	0	75
25	20	20	15
26	5	30	30
27	75	55	33
28	75	45	10
29	5	0	0
30	155	90	150

fibres at operation (Brewer *et al.*, 1973). Fortunately, many patients show objective evidence of improvement in oxygen delivery to the myocardium after operation. This has been shown by exercise electrocardiography (Amsterdam *et al.*, 1970), treadmill exercise tolerance (Knoebel *et al.*, 1971), improvement in myocardial lactate utilisation during atrial pacing (Hammond, 1970; Kremkau *et al.*, 1971; Beer *et al.*, 1972), and increased myocardial oxygen tension (Gardner *et al.*, 1971).

The diagnosis of myocardial infarction after aortocoronary bypass surgery is also fraught with difficulties. Even non-thoracic surgery can be followed by the appearance of Q waves on the scalar electrocardiogram in patients with ischaemic heart disease (Chamberlain and Edmonds-Seal, 1964). Inflammation of the pericardium caused by cardiac surgery may cause T wave changes simulating subendocardial infarction (Brewer *et al.*, 1973). Schrank and his colleagues (1974) have suggested that operation may shift the position of the heart and consequently distort the electrocardiogram and vectorcardiogram. Electrocardiographic changes could also result from alterations in thoracic impedance (Schmitt, 1964). Though Kline and coworkers (1972) have observed transient Q waves during open heart surgery and have suggested that these may be the result of localised hyperkalaemia, this additional source of error is probably irrelevant since postoperative cardiograms were recorded 7 to 10 days after operation.

Only necropsy evidence can provide conclusive proof of perioperative infarction. However, in this study, the vectorcardiogram indicated perioperative transmural infarction which was not apparent on the electrocardiogram. Though the vectorcardiogram diagnosed more cases of infarction than the electrocardiogram, the sensitivity of both methods combined was greater than either alone. It is not surprising that the vectorcardiogram is superior since it provides a more detailed record of the electrical activity of the heart. Schrank and his colleagues (1974) have also noted that after aortocoronary bypass surgery the vectorcardiogram can diagnose anterior infarction which is not apparent on the electrocardiogram, but they found that the vectorcardiogram was not helpful in detecting inferior infarction. In this study, inferior as well as anterior infarction could be detectable only by the vectorcardiogram.

Since the diagnostic sensitivity of the electrocardiogram is related to the size of an infarcted region (Myers *et al.*, 1948, 1949), more extensive infarction about a previously infarcted area may have accounted for the solitary electrocardiographic diagnosis of perioperative anterior infarction when vectorcardiographic evidence of anterior infarction was already present before operation. This result suggests that the recording of preoperative as well as postoperative vectorcardiograms may be necessary if infarction about a previously infarcted area is to be recognised.

The T loop of the vectorcardiogram is less clearly inscribed than the QRS loop. Therefore, in this study, changes in direction of the maximum projections of the T loop were not considered if they were less than 20°. The maximum projections of the T vector do not necessarily represent the same spatial vector and hence quantitative assessment of changes in direction of the maximum spatial vector are not possible. However, large changes in its direction will always be recognised by the method of describing the T loop used in this study.

Alterations in the T loop occurred in 66 per cent of cases. The significance of these changes is difficult to evaluate, but the fact that transmural infarction is a complication of aortocoronary bypass operation suggests that subendocardial infarction can be incriminated in some cases. However, pericarditis resulting from surgery causes identical changes, and changes in repolarisation which follow sudden reperfusion of ischaemic myocardium may be the result of relief of ischaemia rather than of infarction (Smith *et al.*, 1974). It is possible that this may have contributed to the increased incidence of T loop changes in patients showing previous infarction.

References

Amsterdam, E. A., Iben, A., Hurley, E. J., Mansour, E., Hughes, J. L., Salel, A. F., Zelis, R., and Mason, D. T. (1970). Saphenous vein bypass graft for refractory angina pectoris: physiologic evidence for enhanced blood flow to the ischemic myocardium. *American Journal of Cardiology,* **26,** 623.

Battezzati, M., Tagliaferro, A., and Cattaneo, A. D. (1959). Clinical evaluation of bilateral internal mammary artery ligation as treatment of coronary heart disease. *American Journal of Cardiology,* **4,** 180–183.

Beer, N., Keller, N., Apstein, C., Kline, S., Tarjan, E., Carlson, R. G., and Brachfeld, N. (1972). The cardiac hemodynamic and metabolic responses to coronary arteriovenous bypass surgery. *American Journal of Cardiology,* **29,** 252.

Brewer, D. L., Bilbro, R. H., and Bartel, A. G. (1973). Myocardial infarction as a complication of coronary bypass surgery. *Circulation,* **47,** 58–64.

Burch, G. E., Horan, L. G., Ziskind, J., and Cronvich, J. A. (1958). A correlative study of postmortem, electrocardiographic, and spatial vectorcardiographic data in myocardial infarction. *Circulation,* **18,** 325–340.

Chamberlain, D. A., and Edmonds-Seal, J. (1964). Effects of surgery under general anaesthesia on the electrocardiogram in ischaemic heart disease and hypertension. *British Medical Journal,* **2,** 784–787.

Chou, T-C., and Helm, R. A. (1967). *Clinical Vectorcardiography.* Grune and Stratton, New York.

Favaloro, R. G. (1968). Saphenous vein autograft replacement of severe segmental coronary artery occlusion. *Annals of Thoracic Surgery,* **5,** 334–339.

Frank, E. (1956). An accurate, clinically practical system for spatial vectorcardiography. *Circulation,* **13,** 737–749.

Friedewald, V. E., Futral, J. E., Kinard, S. A., Diethrich, E. B., and Flinn, R. S. (1973). Vectorcardiographic changes following saphenous vein coronary bypass surgery. *American Journal of Cardiology,* **31,** 132.

Gardner, T. J., Brantigan, J. W., Perna, A. M., Bender, H. W., Brawley, R. K., and Gott, V. L. (1971). Intramyocardial gas tensions in the human heart during coronary artery-saphenous vein bypass. *Journal of Thoracic and Cardiovascular Surgery,* **62,** 844–850.

Gunnar, R. M., Peitras, R. J., Blackaller, J., Dadmun, S. E., Szanto, P., and Tobin, J. R., Jr. (1967). Correlation of vectorcardiographic criteria for myocardial infarction with autopsy findings. *Circulation,* **35,** 158–171.

Hammond, G. L. (1970). Metabolic response of the myocardium to aortacoronary artery vein grafting. *Circulation,* **41–42,** Suppl. 111-163.

Hugenholtz, P. G., Forkner, C. E., and Levine, H. D. (1961). A clinical appraisal of the vectorcardiogram in myocardial infarction. II The Frank system. *Circulation,* **24,** 825–850.

Kline, S., Apstein, C., Baltaxe, H., and Levine, D. (1972). Left ventricular function after aortocoronary bypass. *Circulation,* **46,** Suppl. II, 23.

Knoebel, S. B., McHenry, P. L., Phillips, J. F., and Jacobs, J. J. (1971). Objective assessment of saphenous vein bypass grafts. *Circulation,* **43–44,** Suppl. 11-187.

Kremkau, E. L., Kloster, F. E., and Neill, W. A. (1971). Influence of aortocoronary bypass on myocardial hypoxia. *Circulation,* **43–44,** Suppl. 11-103.

McConahay, D. R., McCallister, B. D., Hallermann, F. J., and Smith, R. E. (1970). Comparative quantitative analysis of the electrocardiogram and the vectorcardiogram. *Circulation,* **42,** 245–259.

Myers, G. B., Klein, H. A., and Hiratzka, T. (1949). Correlation of electrocardiographic and pathologic findings in posterior infarction. *American Heart Journal,* **38,** 547–592.

Myers, G. B., Klein, H. A., and Stofer, B. E. (1948). Correlation of electrocardiographic and pathologic findings in anteroseptal infarction. *American Heart Journal,* **36,** 535–575.

Perloff, J. K. (1964). The recognition of strictly posterior myocardial infarction by conventional scalar electrocardiography. *Circulation,* **30,** 706–718.

Schatz, I. J. (1973). The need to know. *Chest,* **63,** 82–83.

Schrank, J. P., Slabaugh, T. K., and Beckwith, J. R. (1974). The incidence and clinical significance of ECG-VCG changes of myocardial infarction following aortocoronary saphenous vein bypass surgery. *American Heart Journal,* **87,** 46–54.

Schmitt, O. H. (1964). Averaging techniques employing several simultaneous physiological variables. *Annals of the New York Academy of Sciences,* **115,** 952–975.

Simonson, E., Tuna, N., Okamoto, N., and Toshima, H. (1966). Diagnostic accuracy of the vectorcardiogram and electrocardiogram. A co-operative study. *American Journal of Cardiology,* **17,** 829–878.

Smith, G. T., Soeter, J. R., Haston, H. H., and McNamara, J. J. (1974). Coronary reperfusion in primates. Serial electrocardiographic and histologic assessment. *Journal of Clinical Investigation,* **54,** 1420–1427.

Starr, J. W., Wagner, G. S., Behar, V. S., Walston, A., and Greenfield, J. C., Jr. (1974). Vectorcardiographic criteria for the diagnosis of inferior myocardial infarction. *Circulation,* **49,** 829–836.

Wolff, L., Wolff, R., Samartzis, M. D., Mazzoleni, A., Soffe, A. M., Reiner, L., and Matsuoka, S. (1961). Vectorcardiographic diagnosis. A correlation with autopsy findings in 167 cases. *Circulation,* **23,** 861–880.

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Removal of AC interference from the electrocardiogram

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A method is described for the removal of AC interference from the electrocardiogram in monitors which do not have isolated inputs. The patient's leads are connected to an isolation amplifier which provides isolation between the input and the output and has a high common mode rejection ratio. The output from the isolation amplifier is taken to the electrocardiographic monitor. The isolation amplifier not only provides additional patient safety but also reduces the level of AC interference without interfering with any frequency components in the electrocardiogram.

The presence of AC interference in the electrocardiographic display is a cause for concern in many coronary care units and intensive care units. As well as the hazard of initiating ventricular fibrillation (Raftery *et al.*, 1975), AC interference may also cause difficulty in interpreting the electrocardiogram which may thus be restricted in its usefulness as a diagnostic aid. There are many sources of interference, e.g. poor contact between electrode and skin or the use of long unscreened cables, and these have been outlined elsewhere (Monks, 1971). This paper describes the use of an isolation amplifier after all attempts to remove the source of the AC interference had failed.

The coronary care unit in which this work was carried out was situated in an old hospital building and the monitors did not have isolated input circuitry. After steps had been taken to eliminate all the usual sources of interference, the problem still persisted.

It was decided to investigate the possibility of using an isolation amplifier. The Model 273K from Analog Devices is a unity gain amplifier which provides isolation between input and output grounds and has a high common mode rejection ratio of 115 dB at 60 Hz. Since it has a bandwidth from DC to 2 kHz, it does not interfere with any of the frequency components present in the signal as does a 50 Hz filter, but it does improve the signal-to-noise ratio. Moreover, with older monitors which do not have isolated inputs, it eliminates any earth-borne interference and also provides added patient protection from earth leakage currents. The patient's leads are connected into the isolation amplifier and the output of the isolation amplifier is taken to the electrocardiograph monitor, with the connection between the isolator and monitor as short as possible. The only circuitry to be added is a power supply (two PP7 batteries), a switch, a voltage indicator, and a trimming resistor to calibrate the indicator (Fig. 1). This was incorporated in a metal housing which had a plate at the rear which fits over the bedrail (Fig. 2). This instrument is suitable only for a 3-lead electrocardiogram.

It was recognised during the design of the circuitry and housing that, to be most effective, the instrument should be easy to use. Since the interference presents only intermittently, the instrument is used only as required. When it is necessary to use the isolation amplifier, it is hooked over the bedrail; the patient's lead is removed from the monitor and connected to the isolation amplifier; the lead from the isolation amplifier is then connected to the monitor, and the instrument is switched on. A meter shows that the unit is on as well as indicating the voltage level of the batteries. With our circuitry the batteries require to be changed after 3 weeks of continuous use.

Fig. 3 shows a typical electrocardiogram obtained both with and without the use of the isolation amplifier and indicates the effectiveness of the instrument in removing AC interference from the electrocardiograph display.

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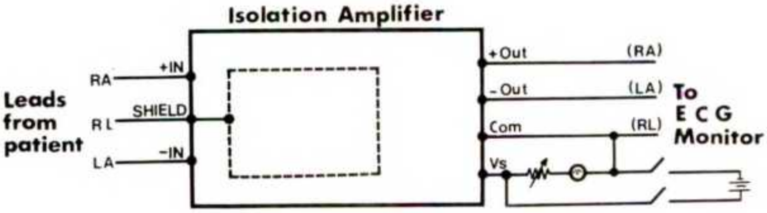

Fig. 1 *Circuit diagram showing the incorporation of an isolation amplifier in lead I of a 3-lead electrocardiogram.*

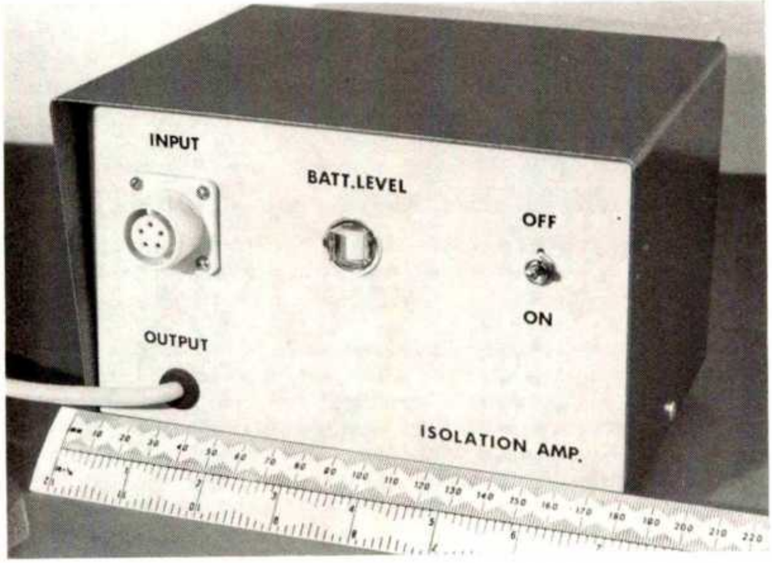

Fig. 2 *Bedside unit which houses the isolation amplifier.*

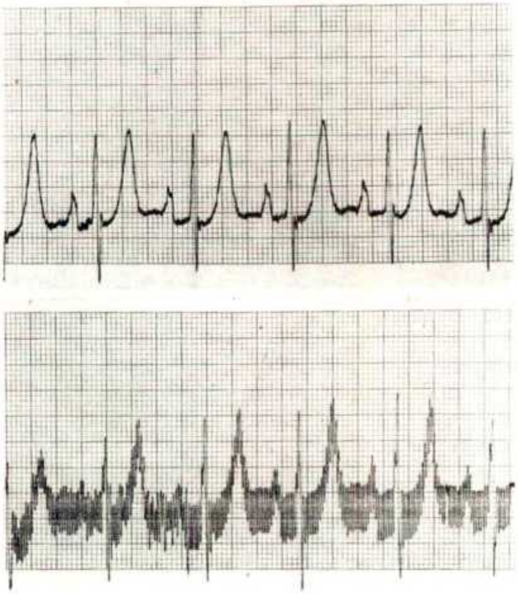

Fig. 3 *Electrocardiograph display with (above) and without (below) isolation amplifier.*
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References

Monks, P. S. (1971). Safe use of electro-medical equipment. *Anaesthesia,* **26,** 264–280.

Raftery, E. B., Green, H. L., and Gregory, I. C. (1975). Disturbances of heart rhythm produced by 50Hz leakage currents in dogs. *Cardiovascular Research,* **9,** 256–262.

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Ruptured bronchial artery aneurysm mimicking aortic dissection

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A patient is presented in whom rupture of a bronchial artery aneurysm produced a clinical picture indistinguishable from an aortic dissection. This case emphasises the importance of considering alternative diagnoses when a patient presents with symptoms typical of a particular condition.

We present a patient in whom the clinical picture closely mimicked aortic dissection, but in whom chest pain, a widened mediastinum, and left haemothorax resulted from haemorrhage from a bronchial artery aneurysm.

Case report

A 56-year-old man, who had had a chronic productive cough for many years, presented with sudden onset of severe tearing central chest pain radiating into his back. On examination he was sweating and in pain with a pulse of 110 and blood pressure of 140/80 mmHg. All peripheral pulses were normal and there was no evidence of aortic regurgitation. The electrocardiogram was normal and the chest *x*-ray film showed a greatly widened mediastinum, a small left pleural effusion and atelectasis, with consolidation at the left base (Fig. 1). During the next 24 hours the patient deteriorated with increasing hypotension and a repeat chest *x*-ray film showed complete opacification of the left hemithorax. Two litres of bright blood was aspirated from the left chest and the patient was transfused with blood, and then transferred to the Brompton Hospital with a preliminary diagnosis of aortic dissection.

ANGIOGRAPHY

The aorta was normal, with no evidence of dissection. A tortuous, greatly enlarged, bronchial vessel was observed running towards the left lower lobe and was selectively cannulated. There was an aneurysm on this vessel 2 to 3 cm from its origin (Fig. 2). Venous return from the area supplied by this vessel was into a pulmonary vein. There were several other smaller, but enlarged, bronchial arteries running to the left lower lobe. In view of the angiographic and clinical findings urgent operation was performed.

OPERATIVE FINDINGS

Left thoracotomy revealed 750 ml fresh blood in the pleural cavity. There was a mass of tense extravasated blood contained in the fascia around the descending aorta and extending forward around the pericardium. The aorta was normal and the bleeding was coming from the bronchial arterial aneurysm shown at angiography. This was immediately below the point where the left vagus gives off its recurrent branch. There were other enlarged bronchial vessels running to the left lower lobe. A left lower lobectomy was performed from which he made an uneventful recovery.

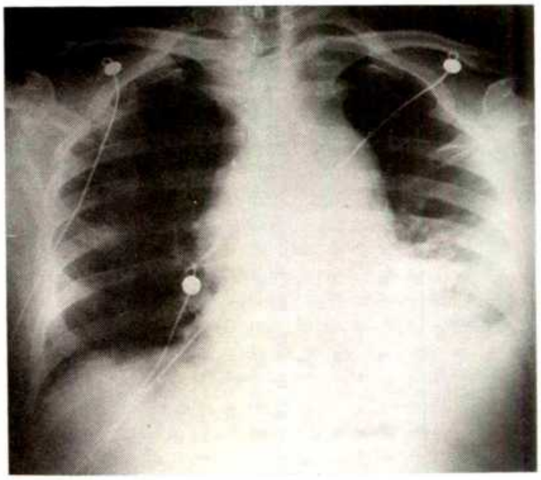

Fig. 1 *Chest* x-*ray film on admission to hospital.*

PATHOLOGICAL FINDINGS

Macroscopical examination showed severe bronchiectasis of the anterior and lateral lung segments of the left lower lobe, which were not sequestrated.

Discussion

Areas of bronchiectasis are often supplied by enlarged bronchial arteries (Turner-Warwick, 1963). Rupture of an aneurysm on such a vessel has not been reported previously though rupture of other intrathoracic aneurysms (De France *et al.*, 1974) and pulmonary arteriovenous fistulae (Brummelkamp, 1961; Dalton *et al.*, 1967) may present with haemothorax.

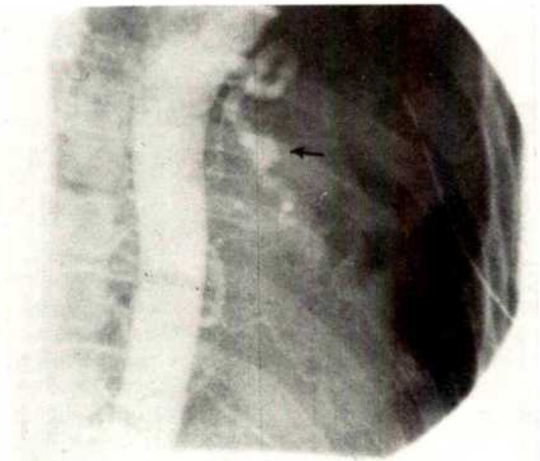

Fig. 2 *Aortogram showing the large bronchial artery and the aneurysm on it (marked by an arrow).*

This patient presented with a clinical picture frequently seen with aortic dissection though the chest pain and mediastinal widening resulted from blood stripping around the aorta from an 'extra-aortic' vessel. This case emphasises the importance of considering alternative diagnostic possibilities, some of which are amenable to urgent surgery, when faced with an apparently typical clinical picture of dissection. It also emphasises that early investigation of suspected aortic dissection is mandatory, both to aid correct management of dissection and to exclude other conditions which may need urgent surgery.

We would like to thank Mr. M. Paneth, who operated on this patient, for his permission to report this case.

References

Brummelkamp, W. H. (1961). Unusual complication of pulmonary arteriovenous aneurysm: intrapleural rupture. *Diseases of the Chest*, **39,** 218–221.

Dalton, M. L., Goodwin, F. C., Bronwell, A. W., and Rutledge, R. (1967). Intrapleural rupture of pulmonary arteriovenous aneurysm. *Diseases of the Chest*, **52,** 97–100.

De France, J. H., Blewett, J. H., Ricci, J. A., and Patterson, L. T. (1974). Massive hemothorax: two unusual cases. *Chest*, **66,** 82–84.

Turner-Warwick, M. (1963). Systemic arterial patterns in the lung and clubbing of the fingers. *Thorax*, **18,** 238–250.

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British Heart Journal, 1977, **39**, 911–913

Prinzmetal's angina

CONSTANTIN B. ATHANASSOPOULOS AND CONSTANTIN G. MAROUTSOS

From the Division of Cardiology of the First Department of Medicine, General State Hospital of Athens, Holargos, Athens, Greece

A 23-year-old man had Prinzmetal's variant angina. After strenuous exercise and isoprenaline infusion the electrocardiogram remained normal and the patient asymptomatic. Coronary angiography gave normal results which remained normal after administration of ergometrine. An injection of methacholine induced an attack.

In 1959 Prinzmetal and co-workers described a 'variant form of angina pectoris' (Prinzmetal *et al.*, 1960). The essential features of this syndrome are chest pain at rest unrelated to exertion and an electrocardiogram characterised by a current of injury pattern during attacks. Occlusion or spasm of a major coronary artery with important reduction of the coronary blood flow has been thought to be the cause of the syndrome.

We report the youngest patient, to our knowledge, with this variant form of angina pectoris in whom a complete haemodynamic and angiographic study did not show any obstruction in his coronaries. The ergometrine test failed to show any significant degree of coronary spasm, though it was possible to reproduce an attack by administration of methacholine.

Case report

A 23-year-old postman was admitted to the General State Hospital of Athens because of severe chest pain which woke him from sleep. The pain started in the midsternal region, radiated to the left chest, and was associated with a moderate degree of dyspnoea. The episode lasted for 15 minutes and disappeared, only to reappear later in the day. The patient had had two similar episodes during the night 7 months earlier.

The family history was non-contributory. The patient had smoked two packets of cigarettes daily for the past three years. Physical examination showed a well-developed man, with a blood pressure of 130/80 mmHg and a heart rate of 64 beats per minute and regular. The jugular venous pressure was not raised and the carotid pulse was normal. The left ventricle was not enlarged clinically and there was no murmur. There was a fourth heart sound heard along the left sternal border.

LABORATORY DATA

The haemoglobin was 16·4 g/dl, with haematocrit 48·2 and WBC 7900/mm^3, with normal differential. A biochemical screening survey, including CK, SGOT, was within normal limits with cholesterol 180 mg/100 ml (4·7 mmol/l). The triglycerides were normal 54 mg/100 ml (0·6 mmol/l). Multiple determinations of aspartate transaminase were within normal limits. VDRL test was normal. A chest *x*-ray film on admission was normal. The electrocardiogram during one of these attacks (Fig. 1A) showed ST elevation in leads I and aVL. Five minutes later when the chest pain had subsided, the electrocardiogram of the Fig. 1B was recorded: this shows ST-T abnormalities mainly in the anterior wall. The electrocardiogram recorded one hour after the attack was normal.

The patient underwent a multistage exercise test on a treadmill. He was able to reach the VII stage 6 m.p.h., 22° incline) without any complaint, electrocardiographic abnormalities suggestive of myocardial ischaemia, or arrhythmia. His heart rate increased normally and reached the expected maximal heart rate for his age (190 beats/min).

Isoprenaline infusion at a rate of 25 μg/min did not reproduce the attack and the electrocardiographic response was normal.

Retrograde left heart catheterisation showed pressures in the left ventricle of 120/9 mmHg, and in the ascending aorta of 120/60 mmHg. Selective right and left coronary angiography in many projections indicated normal coronary arteries (Fig. 2). Ergometrine maleate was then administered intravenously in doses of 0·1, 0·2, and again later 0·3 mg. At no time after the administration of this drug did the patient develop chest pain or electrocardiographic abnormalities. Opacification of each coronary artery after the administration of the drug did

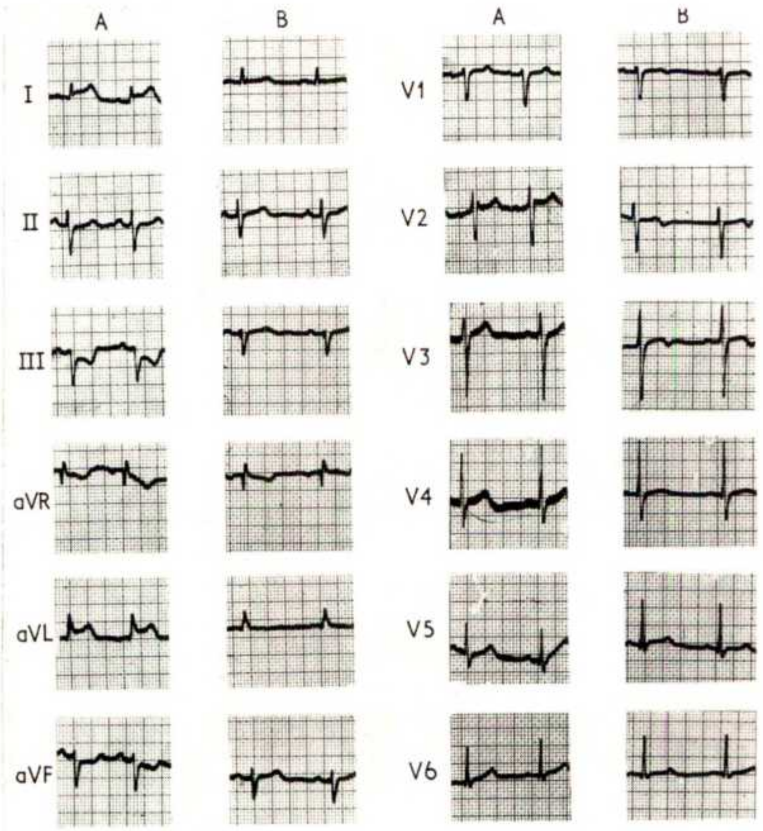

Fig. 1 *Electrocardiogram (A) during attack. (B) 5 minutes later.*

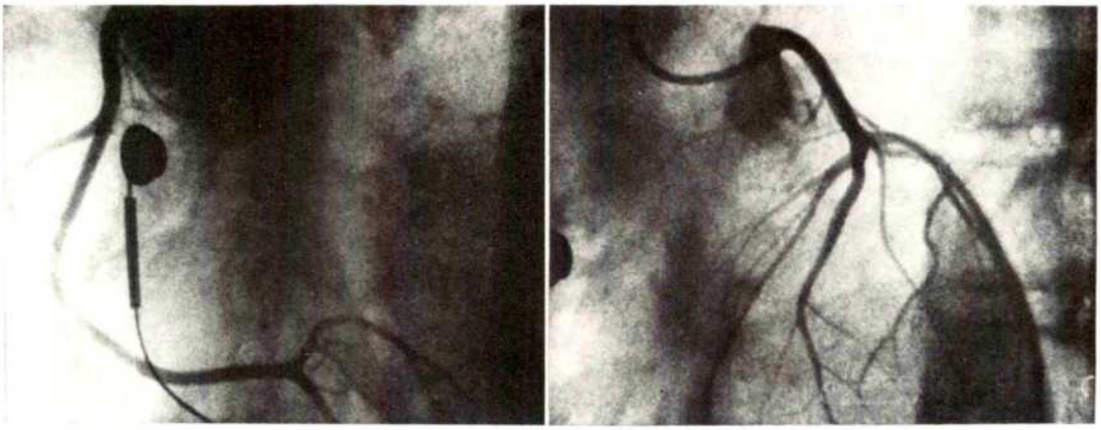

Fig. 2 *Right and left coronary arteriography in the left anterior oblique projection indicates normal coronary arteries.*

not reveal any significant spasm, either diffuse or localised, of the coronary vessels.

A typical anginal attack was elicited 12 minutes after subcutaneous administration of methacholine (0·13 mg/kg) and it was associated with ST segment elevation mainly in leads I and aVL. The pain was relieved immediately after sublingual administration of nitroglycerin.

Discussion

In this young patient all the episodes of pain occurred during the night at rest, a time when myocardial oxygen demand is reduced, and they were not precipitated by strenuous exercise, isoprenaline infusion, or administration of ergometrine maleate.

Cardiac catheterisation done when the patient was not experiencing an attack showed normal coronary arteries and a normally functioning left ventricle. This finding is common in patients with variant angina (Gianelly *et al.*, 1968; Dhurandhar *et al.*, 1972; Cheng *et al.*, 1973; MacAlpin *et al.*, 1973; Endo *et al.*, 1975; Masahiro *et al.*, 1975) as is that of stenosis no greater than 50 per cent in any of the major coronary arteries (Endo *et al.*, 1976). There have been reports of aortocoronary bypass grafts on patients with this syndrome in whom, though the grafts were proved to have good patency after the operation, attacks still continued (Dhurandhar *et al.*, 1972; King *et al.*, 1973; Endo *et al.*, 1976). These observations indicate that an atherosclerotic stenosis or occlusion of a major coronary artery is not always involved in this syndrome.

MacAlpin and his co-workers (1973) were the first to propose the 'spasm theory' as the cause of the symptoms. This suggestion has been supported by several recent reports (Dhurandhar *et al.*, 1972; Oliva *et al.*, 1973; Cheng *et al.*, 1973; Endo *et al.*, 1975, 1976) showing arteriographically that severe coronary arterial spasm was associated with the attacks.

Yasue *et al.* (1974) first reported that they could induce an attack of Prinzmetal's angina by methacholine. Though the methacholine test was not performed on our patient during cardiac catheterisation, the prompt development of typical chest pain and electrocardiographic abnormalities after the administration of the drug suggest coronary spasm as the possible mechanism of the attack. This has been shown lately by Endo *et al.* (1976) during coronary angiography.

The possibility of inducing severe spasm of the coronary arteries and pain in patients with Prinzmetal's type angina with a parasympathomimetic drug suggests that the autonomic nervous system is deeply involved in the pathogenesis of this syndrome.

References

Cheng, T. O., Bashour, T., Kelser, G. A., Jr., Weiss, L., and Bacos, J. (1973). Variant angina of Prinzmetal with normal coronary arteriograms: a variant of the variant. *Circulation,* **47,** 476.

Dhurandhar, R. W., Watt, D. L., Silver, M. D., Trimble, A. S., and Adelman, A. G. (1972). Prinzmetal's variant form of angina with arteriographic evidence of coronary arterial spasm. *American Journal of Cardiology,* **30,** 902.

Endo, M., Hirosawa, K., Kaneko, N., Hase, K., Inoue, Y., and Konno, S. (1976). Prinzmetal's variant angina. *New England Journal of Medicine,* **294,** 252.

Endo, M., Kanda, I., Hosoda, S., Hayashi, H., Hirosawa, K., Konno, S. (1975). Prinzmetal's variant form of angina pectoris: re-evaluation of mechanisms. *Circulation,* **52,** 33.

Gianelly, R., Mugler, F., and Harrison, D. C. (1968). Prinzmetal's variant of angina pectoris with only slight coronary atherosclerosis. *California Medicine,* **108,** 129.

King, S. B., Mansour, K. A., Hatcher, C. R., Silverman, M. E., and Hart, N. C. (1973). Coronary artery spasm producing Prinzmetal's angina and myocardial infarction in the absence of coronary atherosclerosis. *Annals of Thoracic Surgery,* **16,** 337.

MacAlpin, R. N., Kattus, A. A., and Alvaro, A. B. (1973). Angina pectoris at rest with preservation of exercise capacity: Prinzmetal's variant angina. *Circulation,* **47,** 946.

Oliva, P. B., Potts, D. E., and Pluss, R. G. (1973). Coronary arterial spasm in Prinzmetal angina: documentation by coronary arteriography. *New England Journal of Medicine,* **288,** 745.

Prinzmetal, M., Ekmekci, A., Kennamer, R., Kwoczynski, J. K., Shubin, H., and Toyoshima, H. (1960). Variant form of angina pectoris: previously undelineated syndrome. *Journal of the American Medical Association,* **174,** 1794.

Prinzmetal, M., Kennamer, R., Merliss, R., Wada, T., and Bor, N. (1959). Angina pectoris. I. A variant form of angina pectoris. *American Journal of Medicine,* **27,** 375.

Yasue, H., Touyama, M., Shimamoto, M., Kato, H., Tanaka, S., and Akiyama, F. (1974). Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. *Circulation,* **50,** 534.

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British Heart Journal, 1977, **39**, 914–916

Endocarditis as a manifestation of *Chlamydia B* infection (psittacosis)

D. C. DICK, C. G. A. MCGREGOR, K. G. MITCHELL, R. G. SOMMERVILLE, AND D. J. WHEATLEY

From the Departments of Medicine and Pathology, Victoria Infirmary; Department of Cardio-Thoracic Surgery, Mearnskirk Hospital; and Virology Section, University Department of Bacteriology, Belvidere Hospital, Glasgow

A case of Chlamydia B *(psittacosis) endocarditis is described in a patient with no known previous valve disease. After mitral valve replacement a fall in* Chlamydia B *antibody titre occurred. At repeat mitral valve replacement five months later for a paravalve leak no evidence of continuing endocarditis was present. Direct confirmation of infection in the patient's apparently healthy budgerigar was obtained. Aspects of the pathogenesis, diagnosis, and treatment are discussed.*

Endocarditis caused by *Chlamydia B* is rare. We are aware of only two previous well-authenticated reports in which the patient was diagnosed and treated by valve replacement (Birkhead and Apostolov, 1974; Ward *et al.*, 1975). We report a further case in which the diagnosis was established by histology and serology and in which mitral valve replacement was performed.

Case report

A 43-year-old housewife was admitted with a history of tiredness, vague left-sided chest discomfort, and weight loss.

There was no history of previous rheumatic fever or other major illness. A soft apical systolic murmur had been noted one year previously but not subsequently confirmed.

Examination revealed left basal atelectasis, a soft apical systolic murmur as previously noted, and a short diastolic murmur at the left sternal edge. Mild pyrexia was subsequently noted on two occasions during this admission.

Chest *x*-ray film showed a normal cardiac contour, with left lower lobe atelectasis. Haemoglobin was 8·3 g/dl; white count $5{\cdot}4\times10^9$/l; blood film normochromic and normocytic; and erythrocyte sedimentation rate (ESR) 112 mm in the first hour. Repeated blood cultures (six) were negative.

Haemophilus influenzae was isolated in the sputum. She was treated with ampicillin and improved, being discharged after 13 days.

Three months later she was readmitted because of exertional dyspnoea and orthopnoea. She also complained of retrosternal chest pain and a 'loud' heart beat.

She was apyrexial, but now had an apical systolic thrill with a grade 5/6 pansystolic murmur conducted to the axilla. Fine crepitations were heard at the lung bases. The spleen was palpable.

Haemoglobin was 11·5 g/dl and ESR 24 mm in the first hour.

Chest *x*-ray film showed gross cardiac enlargement with pulmonary venous congestion.

The electrocardiogram was normal on admission but T wave inversion in leads III aVF, V2-V3 and ST segment depression in leads V4-V6 developed over the ensuing weeks.

Blood cultures (six) were again repeatedly negative but *Chlamydia B* complement-fixing antibody titre was 1:128. A presumptive diagnosis of *Chlamydia B* endocarditis was, therefore, made.

Further inquiry revealed that the patient had kept an apparently healthy budgerigar for five years and she had been the only member of the household to clean the cage.

Subsequently serology on the other members of the family proved negative. The budgerigar was sacrificed and necropsy showed *Chlamydia B* in stained smears of the liver.

The patient was treated with tetracycline for six weeks but mitral regurgitation was clinically so severe that mitral valve replacement was required.

At operation severe pulmonary arterial and left atrial hypertension were present. The mitral valve was grossly damaged, having two large perforations of the anterior leaflet, ruptured anterior leaflet chordae, and anterior leaflet prolapse. There were no obvious vegetations and the remaining leaflet tissue was only a little thickened. A glutaraldehyde-processed porcine xenograft (Hancock) valve was used as replacement.

The patient made an uneventful recovery. At the time of discharge from hospital *Chlamydia B* complement-fixing antibody titre had fallen to 1:32.

Histology and serology

Microscopically, the valve had lost its normal architecture. The leaflets were thickened and fibrosed, with focal heavy inflammatory infiltration of polymorphs, macrophages, and lymphocytes. Areas of necrosis and haemorrhage were present with perforation at one point. Thrombus at varying stages of organization was present on the leaflet surface.

Modified Giemsa staining of cryostat sections of valve revealed numerous basophilic coccoid bodies (less than 1 μ in diameter) closely resembling typical chlamydial inclusions. Most were present within macorphages, but some were lying free.

Using Macchiavello's method these coccoid bodies were again evident.

Indirect fluorescent antibody staining with the positive human serum confirmed the presence of chlamydiae within the inclusions. Small amounts of nonspecific fluorescence were present throughout the section, but the characteristic bright yellow-green positive fluorescence with the chlamydiae was easily distinguished. Sections stained with the negative control serum were clearly negative.

Direct staining with antihuman Ig:FITC conjugated serum also showed reasonably bright fluorescence, though this was brightest in the envelope and less brillant with the individual chlamydiae within the inclusion. Rabbit anti guinea-pig: FITC conjugate did not show any fluorescing material either in the envelope or chlamydiae within the inclusion. Nonspecific fluorescence was not present.

Subsequent clinical course

Tetracycline was given for four weeks after operation.

About a month after discharge dyspnoea on effort recurred and progressive signs of mitral regurgitation became apparent. Though recurrent chlamydial endocarditis was suspected the antibody titre remained low at 1:28.

Cardiac catheterization 5 months after the initial operation showed severe pulmonary hypertension and raised pulmonary wedge pressure, with prominent 'V' wave. Left ventriculography confirmed fairly severe mitral regurgitation, but it was not clear whether this was central or peripheral to the valve.

At second operation 6 months after the first operation a paravalvar leak was found, caused by tearing out of sutures from the posterior annulus. Though the xenograft valve appeared normal it was removed and replaced by a Bjørk-Shiley prosthesis. Recovery from this operation was uneventful and she was discharged on long-term prophylactic tetracycline. Antibody titre has since shown a further fall to 1 in 8.

Pathological and serological examination of the excised xenograft valve was repeated as previously described and showed no evidence of infection.

Discussion

The incidence of *Chlamydia B* infection in man has shown a steady increase in recent years in the United Kingdom (Communicable Diseases Scotland Weekly Report, 1975). Part of this increase may be attributable to the lifting of restrictions on the importation of psittacine birds in 1966. *Chlamydia B* endocarditis may well be emerging as a more recognized manifestation of the infection.

In previous reports of *Chlamydia B* endocarditis the affected valve has usually shown a congenital abnormality or evidence of previous rheumatic heart disease (Birkhead and Apostolov, 1974; Grist and McLean, 1964; Levison *et al.*, 1971). In the case reported here there was no history to suggest valve disease and at operation no firm evidence of previous valve abnormality was seen. Direct demonstration of *Chlamydia B* infection in the patient's apparently healthy budgerigar confirms the previous suspicion that the domestic budgerigar can be a reservoir of infection for man. Transmission of the disease to our patient probably occurred by inhalation of infected droppings. We now question the wisdom of patients with known valvular heart disease (a group at risk from endocarditis) keeping domestic birds which may be infected with *Chlamydia B.*

Chlamydia B must now be recognized as an additional cause of infective endocarditis. In such cases serological examination for *Chlamydia B* and other unusual organisms such as coxiella should be performed, especially in the presence of negative blood cultures. Though endocarditis was suspected at the time of the initial presentation it is possible that the diagnosis of chlamydial B endocarditis was missed because of failure to appreciate this point. Whether psittacosis infection has a role in the aetiology of chronic valvular heart disease, as Ward (1971) has suggested, is still uncertain.

This case report again raises doubts over the efficacy of present methods of treatment. Though tetracycline in a dose of 1 g/day was administered over a six-week period numerous organisms could be seen in the excised valve. Our experience is similar to that of Birkhead and Apostolov (1974) who failed to eradicate the organism from the aortic valve despite four months' treatment with tetracycline and rifampicin. Recognizing the limitations of present drugs, Oakley (1974) has suggested that tetracycline should be continued indefinitely to prevent relapse.

Valve replacement surgery was performed in this case and postoperatively clinical recovery occurred and was accompanied by a significant fall in *Chlamydia B* complement-fixation antibody titre. This is similar to the experience in the two previous cases described (Birkhead and Apostolov, 1974; Ward *et al.*, 1975). The ideal choice of a suitable valve replacement in such a case is not clear. Though we chose to use a prosthetic valve at the second operation because of doubts regarding infection of the tissue valve, no such infection was demonstrable. Thus a combination of valve replacement surgery and long-term prophylactic chemotherapy may well be the treatment of choice in this manifestation of *Chlamydia B* infection.

We thank Dr. J. Riddell and Dr. T. Semple of the Victoria Infirmary for permission to describe the patient, and Dr. D. J. Taylor of the Department of Veterinary Pathology, University of Glasgow, who performed the necropsy on the budgerigar.

References

Birkhead, J. S., and Apostolov, K. (1974). Endocarditis caused by a psittacosis agent. *British Heart Journal*, **36,** 728.

Communicable Diseases Scotland Weekly Report (1975). **17,** 1.

Grist, N. R., and McLean, C. (1964). Infections by organisms of psittacosis/lymphogranuloma venereum group in the West of Scotland. *British Medical Journal*, **2,** 21.

Levison, D. A., Guthrie, W., Ward, C., Green, D. M., and Robertson, P. G. C. (1971). Infective endocarditis as part of psittacosis. *Lancet*, **2,** 844.

Oakley, C. M. (1974). Infective endocarditis. *British Journal of Hospital Medicine*, **11,** 101.

Ward, C. (1971). Pet birds and acquired chronic valvar disease. *Lancet*, **2,** 546

Ward, C., Sagar, H. J., Cooper, D., and Ward, A. M. (1975). Insidious endocarditis caused by *chlamydia psittaci*. *British Medical Journal*, **4,** 734.

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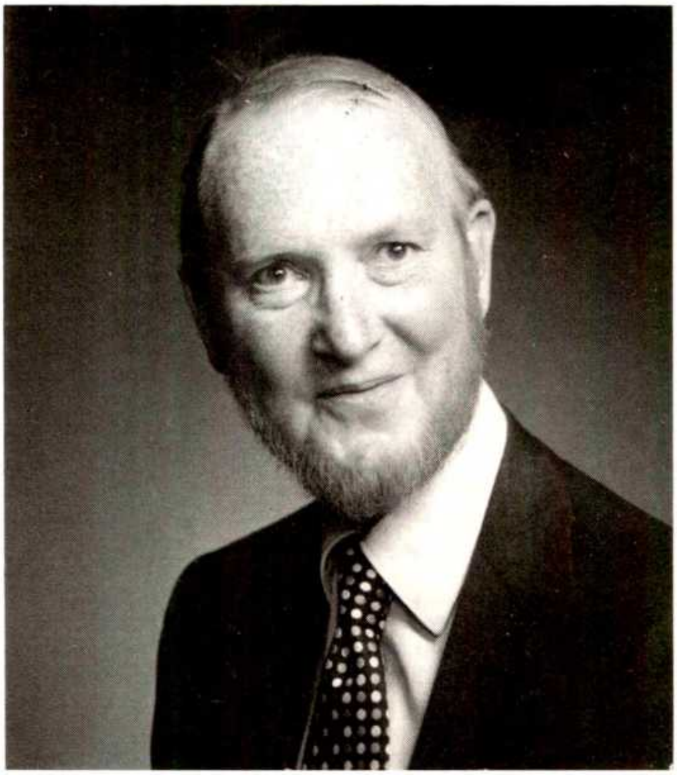
Obituary

British Heart Journal, 1977, **39**, 917–918

Dennis Deuchar



Dennis Deuchar had been Associate Editor of the *Journal* since 1972, when Kenneth Shirley Smith, in his last year as editor, detected his particular abilities. Deuchar's editorial attitude had been shaped by his admiration of clarity. He regarded too many adjectives with suspicion and complex punctuation with irritation. Flowery manuscripts emerged from his attentions pruned of verbosity and with the message clear and easy to follow. The idea of technical editorial perfection delighted him; simplified punctuation, no complicated expressions, easily understood Tables, double-checked statistics, extravagant acknowledgments watered down . . . then a detailed point-by-point report to the author chiding him, complimenting him for original thought, and promising further help, promises he never forgot.

I recall my years with Deuchar with pleasure and gratitude. He was a dedicated editor with a vocational concern for the *Journal*. He had the talent to ease editorial tensions and to foster an atmosphere of relaxed diligence. All of us concerned with the production of the *Journal* remember him with affection.

W. S.

The following tribute was submitted by a colleague and friend:

Dr. Dennis Deuchar, senior physician to the cardiac department at Guy's Hospital, London, died at home on 19 May at the age of 52.

Dennis Deuchar was educated at Bexhill-on-Sea Grammar School and entered Guy's Hospital Medical School in 1943. During his student career his academic brillance was rewarded by several prizes including those in physiology, anatomy, pathology, and the Treasurer's medal for medicine. He qualified MB BS in 1948 and subsequently MRCP in 1951 and MD in 1952.

After house appointments he joined the cardiac department as research student and quickly became active in this rapidly expanding specialty. In parallel with the evolving surgical techniques being established by Russell Brock, Dennis Deuchar—along with Edward Holling and George Zak—was responsible for developing the cardiac catheterisation laboratory at Guy's. This was a time of exciting developments and originality, and Guy's was fortunate that Dennis decided to commit his considerable talents to cardiology.

In 1953 he went to the Johns Hopkins Hospital in Baltimore as the Howard Hughes Foundation research fellow, initiating further original cardiological investigations especially in the development of ballistocardiography, his continued work in this subject later being recognised by his election as president of the Ballistocardiographic Society in 1967. He was the rare true combination of scientist and clinician, and was a founder member of the Biological Engineering Society in 1961. He spent several years as registrar in general medicine and one year as neurological registrar before being appointed to the staff of Guy's Hospital in 1958, joining Charles Baker as consultant cardiologist. He succeeded Dr. Charles Baker and Dr. Ralph Kauntze as physician-in-charge in 1971.

His research work encompassed all aspects of cardiology, and his extensive publications were noted for their clarity of content; they are indeed an accurate record of his outstanding scientific and clinical acumen. Included among his many valuable contributions was his book *Clinical Phonocardiography* published in 1964, which has become a standard work. In addition he was a prominent author in the earliest publications in pacemaking, and electrocardiography, and subsequently investigation of the normal and operated history of congenital heart malformations.

Throughout his career his inquiring mind combined with his mental ability kept him aware of all cardiological and cardiac surgical developments and, more importantly, allowed accurate evaluation of their worth. These were valuable assets in his work as a member of the editorial committee and later as associate editor of the *British Heart Journal* and also editor of *Guy's Hospital Reports.*

I was particularly fortunate in coming under his influence in my training years and later working with him as a colleague. His consistently high clinical standards were, for me, a constant source of professional guidance and reliability.

As a person Dennis was characterised by his optimistic attitude and unobtrusive but keen sense of humour. He naturally responded to enthusiasm but immediately recognised and disliked any form of egotism. Outside medicine he enjoyed London's artistic amenities, particularly classical music and the theatre, and he was also a keen philatelist.

Incredibly, throughout the whole of his medical career from the age of 18, Dennis Deuchar had to cope with serious ill-health, undergoing several courses of radiotherapy and major operations. His character was such that he repeatedly overcame these setbacks with outstanding courage and determination, such that he reached the zenith of his specialty. He was truly the compleat cardiologist, and he will be missed especially at his own hospital where he was admired and respected.

He had a happy and stable family life and is survived by his wife Daphne, and his two sons Ian and Neil, who were all a source of strength to him.

We mourn our loss, but all of us who had the pleasure and advantage of working with him will remember him with affection and pleasure.

ALAN YATES

Correspondence

British Heart Journal, 1977, **39**, 919–920

Comparison of 12-lead and computer-analysed 3-orthogonal-lead electrocardiogram in coronary artery disease

Sir,

The data presented by Murray *et al.* (1976, **38,** 773) do not in my opinion show that the 3-lead-orthogonal electrocardiogram performed more favourably than the 12-lead system. By using formulae recommended by Thorner and Remein (1963) it can be shown that the differences in sensitivity and specificity proportions are not statistically significant. However, I suggest that, in any case, the calculation of these values was based on data from biased samples. The standard of comparison of the 2-lead systems used by Murray *et al.* was the coronary arteriogram, carried out on 102 patients, 77 of whom were categorised as 'ischaemic' and 25 as 'non-ischaemic'. Both the 12- and 3-lead electrocardiograms classified the 102 patients into 4 categories, 'normal', 'ischaemic', 'left ventricular hypertrophy' and 'left bundle-branch block'. Bias was introduced by excluding from the calculations of sensitivity, specificity, and index of merit, the 10 and 13 patients, respectively, diagnosed by the 12- and 3-lead systems as 'left ventricular hypertrophy' and 'left bundle-branch block'. If these are included, the denominators for the calculation of sensitivity and specificity for both systems are 77 and 25, respectively, the numerators remaining as before. The following results are obtained (Table).

The differences in sensitivity and specificity values are, once more, not statistically significant. The only conclusion, in my opinion, which can be drawn from the indices of merit, which are equal at 0·34 on a possible scale of 0 to 1, is that the performance of both systems in the detection of coronary artery disease is equally poor.

Table

Value	*3-lead system*	*12-lead system*
Sensitivity	66% (51/77)	62% (48/77)
Specificity	68% (17/25)	72% (18/25)
Index of merit	$0{\cdot}34 \left(\frac{66+68}{100}-1\right)$	$0{\cdot}34 \left(\frac{62+72}{100}-1\right)$

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Reference

Thorner, R., and Remein, Q. R. (1963). Principles and Procedures in the Evaluation of Screening for Disease. *Public Health Monographs,* 67. U.S. Department of Health, Education and Welfare, Washington.

This letter was shown to Dr. Murray and his co-authors who reply as follows.

Sir,

Thank you for the opportunity of replying to the letter from Dr. Rosamond Gruer concerning our article on 12-lead and computer analysed 3-orthogonal-lead electrocardiograms in coronary artery disease.

We think that Dr. Gruer is wrong in suggesting that our data on sensitivity and specificity are biased. The interpretation of T wave abnormalities on an electrocardiogram can be difficult since they may be the result of a number of factors—and not simply myocardial ischaemia. Clcassical teaching separates T wave abnormalities into two categories—primary and secondary. Primary T wave changes are the result of repolarisation abnormalities which may be caused by myocardial ischaemia, electrolyte imbalance, etc. Secondary T wave changes are a consequence of some other cardiac abnormality such as left ventricular hypertrophy or left bundle-branch block. The difficulty is, however, that some T wave abnormalities may be a combination of the two. In our analysis we thought it advisable to separate the two classes of T wave abnormalities as far as possible and our paper was essentially concerned with the diagnostic accuracy of interpretation of primary T wave abnormalities thought to be caused by myocardial ischaemia.

We did examine the possibility that left ventricular hypertrophy might be accepted as an index of myocardial ischaemia and we provided in the paper alternative estimates of sensitivity and specificity of 3- and 12- lead electrocardiograms in diagnosing coronary artery disease based on this hypothesis. Tracings showing left bundle-branch block were ignored. The 3-orthogonal lead electrocardiogram had an index of merit of 0·51 and the 12-lead electrocardiogram correspondingly had an index of merit of 0·47. These indices are not statistically significantly different. If in addition left bundle-branch block is considered as an index of coronary artery disease corresponding indices are 0·49 and 0·45. If left ventricular hypertrophy and left bundle-branch block are **not** regarded as being indices of myocardial ischaemia, as implied by Dr. Gruer, such electrocardiographic reports are, therefore, taken as compatible with normal coronary arteries. Thus sensitivity falls to 66 per cent and 62 per cent for 3- and 12-lead electrocardiograms, respectively. Dr. Gruer's figures for specificity, however, are wrong. Two patients, one with 3- and 12-lead electrocardiographic evidence of left ventricular hypertrophy and the other with left bundle-branch block, had normal coronary arteries. These patients must be included in the numerator as well as the denominator for the calculation of specificity if left ventricular hypertrophy and left bundle-branch block are **not** indices of coronary artery disease.

Thus:

$$\text{Specificity} = \frac{\text{No. of patients with no electrocardiographic evidence of coronary artery disease}}{\text{No. of patients with no coronary arteriographic evidence of coronary artery disease}}$$

$$= \left(\frac{17+2}{25}\right) \text{ 3-lead} \quad \text{or} = \left(\frac{18+2}{25}\right) \text{ 12-lead}$$

$$= (76\%) \text{ 3-lead} \quad \text{or } (80\%) \text{ 12-lead}$$

This results in indices of merit being 0·42 for both lead systems and not 0·34 as indicated by Dr. Gruer.

Because left ventricular hypertrophy and left bundle-branch block neither clearly indicate the presence of coronary artery disease nor suggest the contrary, it seemed best to us to adopt the approach presented in our paper where the groups are treated separately. To include left ventricular hypertrophy and left bundle-branch block as indices of myocardial ischaemia in a population with chest pain does in our opinion bias data towards a high sensitivity (81% against 77%) at the expense of decreased specificity (68% against 74%). To exclude left ventricular hypertrophy and left bundle-branch block as indices of myocardial ischaemia in a similar population introduces bias against a high sensitivity (66% as against 77%). Specificity is essentially unchanged (76% as against 74%). These figures apply to the 3-lead electrocardiogram; similar trends apply to the 12-lead electrocardiogram data. To **avoid** bias, we presented our results in two ways and the conclusion of the paper was unchanged, as indeed it still is if one takes Dr. Gruer's view.

Our research has always aimed at showing 'that the 3-lead electrocardiogram is clinically as useful as the 12-lead when interpretation is made by automated methods' (Macfarlane *et al.*, 1971). The present study does not alter this view and our conclusion with respect to the diagnosis of coronary artery disease remains as before viz 'This favourable performance provides further justification for the routine use of 3 orthogonal lead electrocardiography'.

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Reference

Macfarlane, P. W., Lorimer, A. R., and Lawrie, T. D. V. (1971). 3 and 12 lead electrocardiogram interpretation by computer. A comparison on 1093 patients. *British Heart Journal*, **33**, 266–274.

British Heart Journal, 1977, **39**, 921–922

Ventricular tachycardia with retrograde conduction

Sir,

In his Letter to the Editor (*British Heart Journal* (1976), **38,** 771) Dr. Marriott criticises the paper of Evans and associates (1974) on 'Ventricular tachycardia with retrograde conduction' and blames the paper's shortcomings on what he calls the authors' 'P-preoccupation syndrome'. Though I agree that the identification of P waves does not by itself prove or disprove the ventricular origin of a tachycardia, it seems to me that the urge to learn as much as possible about the atrial rhythm in an electrocardiogram of tachycardia does not deserve a nosological designation. In many cases this knowledge forms the basis for further information as it did for instance in a case seen by me in 1963.

A 54-year-old man was admitted with a paroxysm of tachycardia. The conventional electrocardiogram showed abnormal ventricular complexes shaped like those seen in left bundle-branch block, with a slightly irregular rate around 200 a minute. In leads II, III, and aVF the tops of most ventricular complexes were notched but the notches were missing in some solitary complexes. An oesophageal lead which was recorded simultaneously with lead II identified the notches as P waves. The PR relation revealed retrograde conduction to the atria with Wenckebach-type block of varying degree. Pressure on the eyeballs did not affect the rhythm of the ventricles but suppressed the retrograde conduction (with disappearance of the notches in lead II) and established atrioventricular dissociation. At this juncture atrial tachycardia was excluded but it was recognised that the differentiation between a junctional and a ventricular tachycardia was not achieved.

Slow intravenous injection of a 10 per cent procainamide solution was started and the oesophageal electrocardiogram was recorded every minute (Fig.); both the atrial and the ventricular rate decreased slowly. During a particular intermediate phase of the injection—when 0·6 g procainamide were injected—the relative timing of the P and R waves allowed every fifth sinus impulse to capture the ventricles and to produce a ventricular complex which later, when sinus rhythm was restored, proved to be identical with that of sinus beats. Careful inspection of the tracing taken after the injection of 0·4 g procainamide showed a solitary fusion beat; its nature was suggested by the intermediate shape of the ventricular complex and was confirmed by the timing of the preceding P wave. Neither before the injection nor in its final phases were the conditions favourable to the appearance of capture or fusion beats and none was found. Only the monitoring of the oesophageal tracings during procainamide injection led to the detection of the transient period in which fusion and capture beats could be expected and occurred. The therapeutic procedure yielded the marginal benefit of a diagnostically useful sign (Puech *et al.,* 1970), which brought the diagnosis one step nearer to certainty.

I am aware of the objections to overestimation of ventricular captures and of fusion beats as supposed final proof of the ventricular origin in tachycardias. Objections can be raised equally to an overreliance upon QRS morphology as the final criterion of differential diagnosis; both approaches involve statistical probability and call for every bit of additional evidence. The unearthing of P waves has a special attraction for the routine-bound clinician: in our science fiction dreams we of the pre-His-electrogram generation were fascinated by the cardiac impulses as they emerged, propagated, entered, re-entered to and fro, and collided all over the myocardium. In the waking hours all that reached our senses from this animated world were the two signals of the atrial and the ventricular deflection in our tracing. From this meagre material deductive thinking had to reconstruct mechanisms of abnormal cardiac rhythm much as a palaeontologist reconstructs the shape of an extinct animal on the evidence of single bones. Every additional bone is precious. Therefore, the electrocardiographer who indulges in P detection should not feel neurotically guilty even when the immediate practical application of his findings is not guaranteed. 'One never knows what findings of importance may be uncovered in the course of a quest after the truth.' (Marriott and Myerburg, 1974.)

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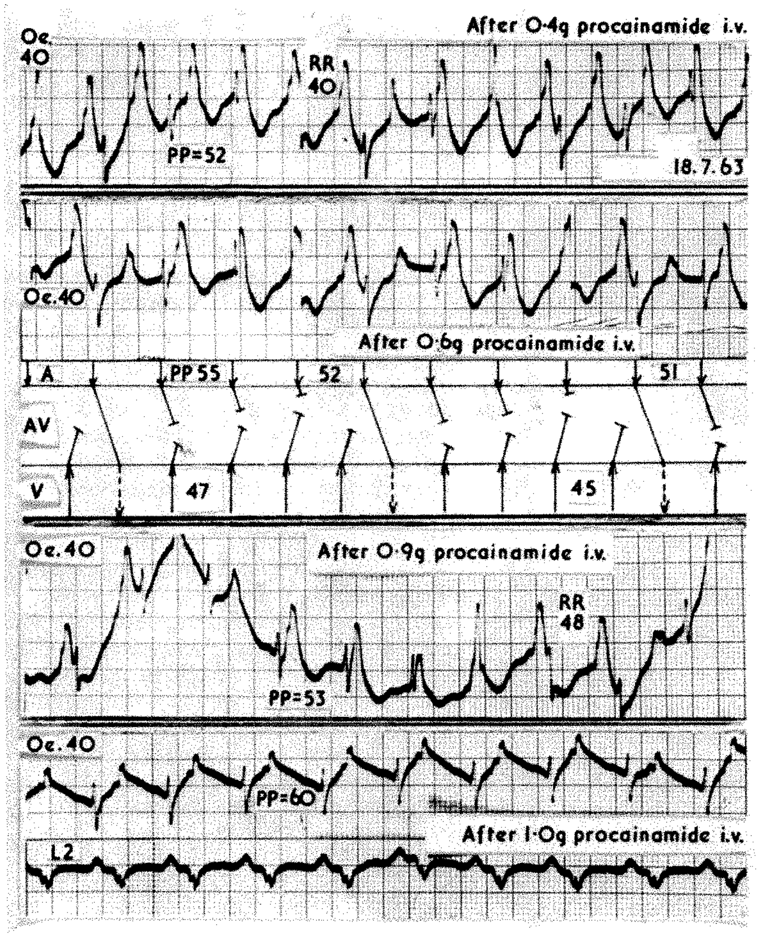
Oe. 40
After 0·4g procainamide i.v.
RR 40
PP=52
18.7.63
Oe.40
After 0·6g procainamide i.v.
A
PP 55
52
51
AV
V
47
45
Oe.40
After 0·9g procainamide i.v.
RR 48
PP=53
Oe.40
PP=60
After 1·0g procainamide i.v.
L2

Fig. *Atrioventricular dissociation in 'almost certain' ventricular tachycardia. Panels 1–3: Strips of oesophageal lead (40 cm from the nares), taken at the end of intravenous injection of 0·4, 0·6, and 0·9 g procainamide. Top panel, centre: one fusion beat. 2nd panel: three capture beats (diagram). Bottom panel: simultaneous record of the oesophageal lead and lead II taken after the injection of 1·0 g procainamide and the restoration of sinus rhythm.*

References

Evans, G. L., Charles, M. A., and Thorrsvard, C. T. (1974). Ventricular tachycardia with retrograde conduction. Simplified diagnostic approach. *British Heart Journal*, **36**, 512–515.

Marriott, H. J. L., and Myerburg, R. J. (1974). Recognition and treatment of cardiac arrhythmias and conduction disturbances. In *The Heart*, 3rd ed., p. 536. Chief Editor: J. W. Hurst. McGraw-Hill, New York.

Puech, P., Grolleau, R., Fijac, E., and Posner, J. (1970). The diagnosis of supraventricular arrhythmias and the differentiation between supraventricular tachycardias with aberrant conduction and ventricular tachycardias. In *Symposium on Cardiac Arrhythmias*, p. 211. Ed. by E. Sandøe, E. Flensted-Jensen, and K. H. Olesen. AB Astra, Södertälje, Sweden.

British Heart Journal, 1977, **39**, 923-933

Proceedings of the British Cardiac Society

THE 56th ANNUAL GENERAL MEETING of the British Cardiac Society was held at The Rupert Beckett Lecture Theatre at Leeds University on Wednesday and Thursday, 13 and 14 April 1977. The President, W. SOMERVILLE, took the Chair during private business. At the scientific sessions the Chair was taken by W. WHITAKER.

Loss of electrically active myocardium during anterior infarction in man

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A method of 72 point praecordial electrocardiographic mapping of RS ratio changes and the appearance of Q waves during acute myocardial infarction has been developed. Serial praecordial electrocardiographic mapping in 20 subjects with no evidence of cardiovascular disease showed that, when each patient was at rest and in the same position, pathological Q waves could not be found and the RS ratios varied less than ±5 per cent. Changing abnormal areas of R wave loss, RS ratio change, and Q waves could be outlined in patients with anterior myocardial infarction.

The serial changes in RS ratio showing loss of R wave in 40 patients with uncomplicated anterior infarction showed that the regional loss of electrically active myocardium progressed rapidly and was complete within 6 hours from the onset of chest pain.

In these patients creatine kinase -MB (CKMB) activity (m units ml^{-1}) was first detected in the plasma between 6 and 10 hours and reached a peak at $19{\cdot}5 \pm 1{\cdot}7$ hours (mean ± 1SD) after the onset of chest pain.

In this group of patients the regional loss of active myocardium occurred before the appearance of MBCK activity in the plasma. This time course and the relation to the release of plasma MBCK activity is important when considering interventions aimed at salvage of myocardium during infarction of the heart.

Myocardial scintigraphy on a coronary care unit using mobile gamma camera; an aid to positive diagnosis in patients with chest pain

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Sixty-one cardiac scans were performed on patients admitted with chest pain to the coronary care unit. Imaging was performed between 4 hours and 8 days after the onset of chest pain, 2 hours after injection of Tc^{99m} stannous pyrophosphate using a mobile gamma camera at the bedside.

In a control group of 37 patients with clinical, electrocardiographic, and enzymic criteria typical of infarction, 34 had positive scans (24 out of 25 transmural and 10 out of 12 subendocardial). Of a group of 11 patients with chest pain without infarction, 9 had negative scans. These results, obtained by 5 observers independently without knowledge of the diagnosis, are highly significant ($P < 0{\cdot}001$).

Three patients with clinical evidence of infarction, but conduction defects making the electrocardiogram difficult to interpret, had positive scans.

Of 13 patients with crescendo angina, 10, including a further 5 preoperative patients, had positive scans. None of these 13 had new electrocardiographic abnormalities or raised enzymes. These results support the recent concept that patients with crescendo angina may have ongoing myocardial necrosis undetectable by conventional methods. The dividing line between crescendo angina and subendocardial infarction appears artificial.

Influence of location of myocardial infarction on right and left ventricular ejection fraction

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Left ventricular ejection fraction can be estimated from the high frequency fluctuations in count rate over that ventricle after the intravenous injection of a bolus of radioisotope. Since no assumptions are made about ventricular shape, the technique is applicable in the presence of wall motion abnormalities which may accompany myocardial infarction. It is theoretically also a valid method for the estimation of right ventricular ejection fraction, which is difficult to assess using standard radiological methods.

Right and left ventricular ejection fractions were estimated in 31 subjects. In 10 normal controls the mean left ventricular ejection fraction was 0·68 ± 0·06 (SD) and the mean right ventricular ejection fraction was 0·61 ± 0·05. Left ventricular ejection fraction was depressed in anterior (0·48 ± 0·06), anteroinferior (0·41 ± 0·05), inferior (0·50 ± 0·07), inferoposterior (0·54 in 3 cases), and posterior (0·50 in 1 case) infarction. Right ventricular ejection fraction was depressed in inferior (0·47 ± 0·05), anteroinferior (0·48 ± 0·09), inferoposterior (0·53 in 3 cases), and posterior (0·54 in 1 case) but not anterior (0·58 ± 0·08) infarction.

Right ventricular ejection fraction, which can be determined simultaneously with that of the left ventricle, is a potentially useful measure of right ventricular involvement in myocardial infarction.

99m-Tc imidodiphosphate; a new radiopharmaceutical for positive myocardial infarction imaging

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To demonstrate the uptake of 99m-Tc imidodiphosphate (99m-Tc IDP) by damaged myocardial cells, acute myocardial infarction was induced in 10 rats by ligation of the left coronary artery; they were imaged serially with a standard 11½ in 37PM tube scintillation camera after injection of 500μCi of the tracer. A control group underwent thoracotomy without infarction. Correlation was made between radiopharmaceutical uptake and the degree of myocardial damage determined histologically from sections of the entire heart of the sacrificed animals.

Twenty patients with electrocardiographic and enzymatic evidence of acute myocardial infarction were imaged in the coronary care unit with a mobile low energy (Pho Gamma) scintillation camera 60 minutes after injection of 10 mCi of 99m-Tc IDP. Serial images, obtained for 8 days after admission, showed a high target to non-target ratio. Blood clearance data were obtained in another group of patients undergoing whole body bone scanning with the same radiopharmaceutical. Comparison with similar data for other 99m-Tc labelled phosphates in clinical use (PP, PYP, EHDP, MDP) showed rapid blood clearance.

These results and their relevance in patient management suggest that 99-mTc IDP, not previously reported in clinical use, is at present the best radiopharmaceutical available for positive myocardial imaging.

Flux of plasma lipoproteins into human arterial intima *in vivo*

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A role of plasma lipoproteins in atherogenesis is supported by epidemiological data and by analyses of arterial lipoprotein levels. In an ongoing study we are measuring the net rates of lipoprotein entry into arterial intima from plasma in patients undergoing arterial surgery.

Fourteen patients (serum cholesterol 3·06 to 9·9 mmol/l triglyceride 1·27 to 3·84 mmol/l), undergoing aortic or coronary surgery were studied, using autologous ^{125}I low density lipoprotein (LDL) and ^{131}I very low density lipoprotein (VLDL). Lipoproteins were injected 4 hours to 9 days before operation. From plasma and aortic intimal radioactivity net fluxes were determined for apolipoprotein B (apoB).

ApoB from LDL and VLDL, and ApoB from VLDL enter aortic intima. Vein intima showed insignificant activities.

Net flux of LDL-apoB into intima, per unit area, was directly correlated with plasma LDL levels. VLDL-apoB flux was most closely correlated, directly, with fractional catabolic rate of plasma VLDL. LDL-apoB net flux was also inversely related to plasma HDL concentration. These findings suggest that LDL enters the artery at a rate proportional to its plasma concentration, and that VLDL or its metabolic products also enter the intima.

Anatomical correction for classic transposition of the great arteries

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Three patients aged 20 months, 4 years, and 6 years with classic transposition of the great arteries had successful surgical correction by switching the great arteries and coronary arteries into their correct anatomical positions. A fourth patient, aged 10 days, whose left ventricular pressure was 25 mmHg after Rashkind had banding of the pulmonary artery and a left Blalock shunt to raise the left ventricular pressure to systemic levels as a preparation for subsequent arterial correction.

The first three patients were selected for this procedure because the left ventricular pressure was at systemic level because of a large ventricular septal defect in 2, and a duct and atrial septal defect in 1. Removal of an additional subpulmonary fibrous ring was accomplished after transection of the pulmonary artery in 2 patients.

In the first 2 patients where the ventricular septal defects were closed, the pulmonary artery pressure fell to 30 to 35 mmHg, right ventricular hypertrophy regressed, and the patients remain well 6 to 15 months later. In the third child, a large ventricular septal defect was left open after closure of a duct because of high pulmonary vascular resistance and represents a palliative anatomical correction. The child's effort tolerance improved and the systemic arterial saturation rose from 66 to 81 per cent.

If this logical surgical treatment for transposition of the great arteries has a place, the basic management of the infant must change.

Two-stage operation for anatomical correction of transposition of the great arteries with intact ventricular septum

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Anatomical correction of transposition of the great arteries (TGA) by reattaching the aorta, pulmonary, and coronary arteries to the appropriate ventricles is now feasible. The presence of a well-developed posterior ventricle, capable of supporting the systemic circulation (as in patients with additional ventricular septal defect) is essential for the success of the operation. In patients with TGA and intact ventricular septum, the posterior ventricle fails to develop, thus precluding the possibility of primary anatomical correction. To get over this difficulty we have used a first stage operation which consists of banding the pulmonary artery, aortopulmonary shunt proximal to the band, using a homologous vein graft, and atrial septectomy. This procedure was performed in an infant with TGA at the age of 2 weeks. The peak systolic RV/LV pressure ratio which was 3/1 before the first stage, changed to 1/1 at the time of operation and was found to be 1·3/1 after 3 months. Anatomical correction was then performed at the age of 6 months with a smooth postoperative recovery. The child has been followed up for 3 months. Postoperative left ventricular function, assessed by echocardiography and repeat left ventriculography, was found to be normal.

It is concluded that preliminary banding of the pulmonary artery with aortopulmonary shunt can render children with TGA suitable for anatomical correction.

Composite pericardial xenograft for right ventricular outlet reconstruction

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Glutaraldehyde treated composite pericardial xenografts were used between May 1972 and November 1976 for reconstruction of the right ventricular outlet in 24 patients with complex congenital cardiac anomalies. In 22 patients a diamond shaped pericardial patch with a monocusp valve was used while in 2 a complete conduit with a three-cusp valve was inserted. There were 3 early and 1 late (8 months) death unrelated to the xenograft. The 20 long-term survivors have been followed up for a total of 828 months (mean 46). Symptomatically all patients are now in grade I (NYHA).

Pressure recordings at the conclusion of operation showed that the right ventricular systolic pressure varied between 25 and 55 mmHg (mean 36) and the maximum gradient across the pericardial xenograft was 20 mmHg.

Haemodynamic studies were performed in 9 patients, 2 to 49 months (mean 20) after operation. Right ventricular systolic pressure varied between 25 and 60 mmHg (mean 40) and the gradient across the xenograft was between 5 and 20 mmHg (mean 12). Angiography revealed normal mobility and function of the pericardial valve cusps and mild to moderate pulmonary regurgitation.

The very good record of patients' survival, lack of xenograft calcification, and maintenance of function with the passage of time, fully justify the continued clinical use of the pericardial xenograft for right ventricular outlet reconstruction.

Side-to-side cavo-pulmonary anastomosis for the palliation of 'primitive ventricle'

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The Glenn operation, end-to-side anastomosis of the pulmonary artery to the superior vena cava, is an established palliative procedure for patients with 'primitive ventricle and pulmonary stenosis'.

Experience with 14 cases during the past 8 years suggests that side-to-side anastomosis is preferable. As the pulmonary artery is not divided the shunt goes to both lungs. The postoperative course is much easier and the clinical result appears much better. It may be that preservation of pulsatile flow to both lungs is helpful.

During the earlier years the operation was done only in patients with extremely low damped pulmonary artery pressure, but more recently pressures up to 30/10 mmHg have been accepted, that being the pressure in a neonate operated on at 16 days with a most satisfactory result.

This operation, like the Glenn, reduces the output of the single effective ventricle rather than increasing it greatly as does a systemic to pulmonary artery shunt.

The anastomosis appears to grow with the child and the pulmonary artery pressure is open to clinical observation and catheterisation.

The operation forms a suitable preliminary to the Fontan procedure.

Long-term clinical follow-up of patients with pericardial xenograft valve replacement

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Glutaraldehyde stabilised pericardial xenografts were used between March 1971 and December 1976 for single valve replacement in 285 patients (176 aortic, 106 mitral, and 3 tricuspid). The 267 hospital survivors have been followed up for 9101 months (mean 36).

Actuarial analysis showed a projected survival rate (± SE) at 6 years of 90·1 (± 7·5) per cent for patients with aortic and 92·1 (± 4·9) per cent for patients with mitral replacement. The embolic rate was 0·58 and 1·7 episodes per 100 patient years respectively, without anticoagulant treatment.

Haemodynamic studies were performed in 30 patients with aortic replacement (AR) and in 27 patients with mitral replacement (MR) at mean intervals of 43·4 (range 27 to 59) and 40·2 (24 to 59) months after operation respectively. Significant haemodynamic improvement was noted in both groups. The mean peak systolic gradient in patients with AR was 6·4 mmHg at rest and 9·6 mmHg on exercise. The mean diastolic gradient in patients with MR was 6 mmHg at rest and 15 mmHg on exercise.

Comparison of data from sequential haemodynamic studies performed in 13 AR and 6 MR patients showed no significant changes between the circulatory parameters recorded at 10 and 42 months postoperatively.

Symptomatically 96 per cent of patients are now in grade I (NYHA). Microscopy demonstrated maintenance of structural integrity of all pericardial xenografts examined.

The very good record of patients' survival and the low embolic rate fully justify the continued clinical use of the pericardial xenograft for valve replacement.

Clinical and haemodynamic assessment of Hancock stent mounted heterograft in mitral position

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Fifteen patients were assessed clinically and by cardiac catheterisation 4 to 32 months (mean 15 months) after isolated mitral valve replacement (12) or mitral and aortic valve replacement (4) with stent mounted porcine heterografts.

After operation, 12 of the patients improved from grades III (9 patients) and IV (3 patients) to grade I (9 patients) and II (3 patients). Three patients remained in grade III, one of whom had severe aortic regurgitation. A mid-diastolic murmur was present in 6 patients. One patient had a systolic murmur suggesting mitral regurgitation.

At cardiac catheterisation the average values were: mean pulmonary artery pressure 30 mmHg (15 to 40), mean pulmonary artery wedge pressure 2 mmHg (9 to 32), left ventricular end-diastolic pressure 18 mmHg (8 to 27), AVO_2 difference 4·1 ml per cent (2·9 to 5·6), cardiac index 2·7 ml/

min per m^2 (1·4 to 4·1), ejection fraction 51 per cent (10 to 74).

Angiography showed a competent prosthesis in 13 patients and moderate mitral regurgitation in one. In one patient the mean mitral valve diastolic gradient was 15 mmHg and in one it was not measured. In 13 patients it averaged 4·7 mmHg and values tended to be highest in those with smaller prostheses. In 6 patients with a mid-diastolic murmur it averaged 4·0 mmHg.

It is concluded that mitral stent mounted porcine heterografts are satisfactory in the majority of patients, but the smaller prostheses give larger gradients and in some patients the valve is obstructive. Some patients have a mid-diastolic murmur which does not indicate prosthetic valve malfunction.

Multistage treadmill testing in selection of patients for coronary arteriography

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The formidable number of potential candidates for coronary arteriography demands the development of a diagnostic screening technique which will identify those patients in whom this investigation is most likely to be helpful.

We have studied 320 patients by subjective maximal treadmill testing using the Bruce protocol. In this paper we present the results obtained in 50 patients correlated with the findings on coronary arteriography and left ventriculography.

All patients in whom there was ST segment displacement of greater than 2·00 mm had either triple vessel disease or grossly abnormal left ventricular wall movement. ST segment displacement of less than 2·0 mm did not differentiate between single, double and triple vessel disease.

A fall in systolic blood pressure below the resting level was not diagnostic of left main stem disease.

When ST segment displacement was correlated with the percentage change in heart rate × percentage change in mean arterial blood pressure the accuracy of diagnosis was greater than with ST segment displacement alone. Using these values no patient with coronary artery obstruction of less than 50 per cent in any vessel had a positive treadmill result, and the number of false negative diagnoses was reduced from 10 to 2 per cent.

It is concluded that multistage treadmill testing is a useful, non-invasive procedure in the selection of patients for coronary arteriography.

Induction of coronary artery spasm with ergometrine

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Some patients with cardiac pain are found to have either normal coronary arteries or minimal obstructive disease ($<50\%$). We investigated 27 such patients, 18 men and 9 women, aged 19 to 62. Up to 500 μg ergometrine maleate was administered intravenously in divided doses and the coronary arteriogram repeated. Two patients developed their typical pain, distinct ST segment changes, and diastolic narrowing of the right coronary artery of 71 and 64 per cent of the original measurement, respectively.

One patient developed 60 per cent narrowing of the right coronary artery and experienced typical pain without ST segment change. A further 3 patients had narrowing of all 3 coronary arteries by an average of 45 per cent of the original measurement (range 27 to 62%) but did not develop chest pain or electrocardiographic abnormalities in the leads being monitored. Isordil produced prompt vasodilatation in all cases to an average of 114 per cent of control.

We conclude that coronary artery spasm may be the cause of cardiac pain in some patients and that diagnosis may be assisted with the use of ergometrine. There are also clear therapeutic implications.

Coronary artery ectasia

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Ten male patients aged 37 to 71 were found to have coronary artery ectasia in a total of 850 studied with coronary arteriography.

Nine patients were severely incapacitated by angina and one by paroxysmal ventricular tachycardia. Six had had one or more myocardial infarcts before study. Five patients had hyperlipoproteinaemia but only 2 had a family history of coronary artery disease. Nine had been heavy smokers. Associated cardiovascular disease was subvalvar mitral regurgitation in 2 and hypertension in 2. Pernicious anaemia was found in 2 cases, 1 of whom had a collagen vascular disease.

The most common ectatic vessel was the circumflex in 6 patients followed by the right coronary artery in 4. Only 1 case had isolated ectasia with other coronary arteries normal. All others showed severe disease or total occlusion of the non-ectatic vessels. Only 1 patient had an ectatic left anterior descending coronary artery and a pacing-lactate study showed abnormal lactate metabolism in this case.

Coronary artery ectasia is most commonly a variant of occlusive arteriosclerotic coronary artery disease. Though said to have a poor prognosis, 9 patients followed for up to 2 years are still alive.

Correlation of regional myocardial wall motion with regional perfusion in stable angina pectoris using dual nuclide scintigraphy

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Myocardial wall motion is intimately linked to myocardial perfusion. This relation has been explored in a non-invasive manner during regional ischaemia in patients with stable angina pectoris. Using thallium-201 (Tl^{201}) as a marker of regional myocardial perfusion and technetium-99m (Tc^{99m}) labelled autologous red cells as a central blood pool tracer, gated cardiac scintigrams were performed immediately after exercise thallium scintigrams in 25 patients with coronary artery disease.

Segmental quantification of thallium uptake in the left ventricle was correlated with segmental left ventricular wall motion in two planes. A linear relation was found between the degree of myocardial tracer uptake and corresponding myocardial wall motion ($r = 0{\cdot}70$, $P < 0{\cdot}001$). Regional akinesia was always associated with absent thallium uptake and the corollary that normal wall movement was never associated with absent thallium uptake was also true.

Practically this relation may be used to predict the likelihood of segmental necrosis or segmental ischaemia when defects are seen in exercise thallium scintigrams permitting economy and administrative convenience by dispensing with repeat rest thallium scintigrams.

Finally gated cardiac scintigraphy allowed visualisation of right ventricular movement not provided by thallium scintigraphy enabling right coronary occlusive disease to be predicted accurately in 4 patients increasing the sensitivity of diagnosis.

Unstable angina: clinico-arteriographic correlation and late results of surgical treatment

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C. De Gasperis, M. Towers, and M. Yacoub
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Between June 1973 and December 1976, 54 patients with unstable angina (defined by a set of rigid clinical criteria) were studied. There were 50 men and 4 women with a mean age of 53·4 years. Forty patients (75%) had previously had stable angina, the remaining 14 (25%) presented with unstable angina of less than 2 months duration. Twenty-three patients (43%) had a previous myocardial infarction. Forty-eight patients were investigated during the acute phase at Harefield Hospital with no mortality. Of these, 7 patients (15%) were investigated during intra-aortic balloon counter pulsation (IABC) because of persistent severe angina. Fifty-three (98%) had severe narrowing of either the left main coronary artery or the left anterior descending artery, or both. Additional severe lesions in other arteries occurred in approximately 80 per cent. Thirteen patients (24%) required IABC before induction of anaesthesia. A total of 141 grafts was required in the 54 patients (2·8 grafts per patient). There were 2 early deaths (3·7%) and 2 late deaths (3·7%). Follow-up extended between 3 and 40 months (mean 19 months). Perioperative myocardial infarction occurred in 5 patients (9·3%). Thirty-seven patients (80%) were asymptomatic and 9 patients (20%) improved. Thirty-one patients (78%) returned to full-time work. Late myocardial infarction occurred in 2 patients (40%). Thirty-seven patients (75%) were reinvestigated by repeat coronary, graft, and left ventricular angiography between 2 weeks and 40 months (mean 19·3 months). The overall patency rate was 90 per cent. Left ventricular function, as assessed by ejection fraction and pattern of contraction, showed improvement in the majority of patients. It is concluded that patients with unstable angina can be investigated safely during the acute phase, and usually have severe lesions in the left main or proximal left anterior descending artery. The early and late results of surgical treatment have been encouraging. IABC is a valuable aid in the management of these patients.

Long-term follow-up of 100 per cent of 362 consecutive coronary bypass patients

D. G. Greene, I. L. Bunnell, D. T. Arani,
R. N. Tandon, W. T. Zimdahl, J. M. Bozer,
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The first 362 patients at the Buffalo General Hospital to have coronary bypass surgery uncomplicated by ventricular resection, valve replacement, mammary implantation, or congenital heart lesions have been followed for a minimum of 1 year and to death or to the cutoff date. The 5-year survival rate was 87·3 per cent, and was unaffected by the presence of 1-, 2-, or 3-vessel involvement, unstable angina, or history of a previous myocardial infarction. The presence of a main left coronary artery lesion or of an ejection fraction less than 0·40 affected survival adversely. Patients with 2- and 3-vessel disease did significantly better than analogous groups from the published reports who had been treated medically. After the 28 deaths in the first year survival was statistically indistinguishable from an age- and sex-matched sample of the U.S. population. In 147 patients chosen to match Gazes's series of medically treated unstable angina the survival was better with surgery. In 19 of these patients whose findings fit the criteria of Gazes's high-risk group survival was also better with surgery. The 30-day mortality in the initial Buffalo General Hospital series, 3·7 per cent, has since fallen to 1·6 per cent in the next 515 cases.

Assessment of myocardial damage after coronary surgery

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The electrocardiograms and left ventriculograms of 40 patients before and up to 36 months after coronary surgery have been subjected to detailed analysis. Ejection fraction in the group as a whole did not change significantly ($0{\cdot}64 \pm 0{\cdot}13$ to $0{\cdot}62 \pm 0{\cdot}13$).

In group A ($N=12$) who had abnormal preoperative function ($EF < 0{\cdot}58$) there was a significant improvement in ejection fraction ($0{\cdot}49 \pm 0{\cdot}10$ to $0{\cdot}55 \pm 0{\cdot}07$). Using a change of 0·10 in ejection fraction as indicating a significant change, 7 patients in group A improved and 2 deteriorated after surgery. Wall motion analysis indicated that the changes only took place in preoperatively abnormal areas. In those patients with normal preoperative function (group B, $N=28$), 5 patients developed significant localised wall motion abnormalities. In 2 of these new inferior infarcts, and in 2 extensions of inferior infarcts, were seen electrocardiographically. In one patient a significant inferior wall motion abnormality appeared without electrocardiographic abnormalities. Three septal infarctions were not visualised on right anterior oblique ventriculograms.

After coronary surgery, deterioration in left ventricular function was seen either by extension of previous myocardial damage or by new infarcts. There was no evidence of global depression of function.

The incidence of myocardial damage when assessed by electrocardiogram and wall motion abnormalities in this group was 25 per cent.

Mechanism of left atrial filling in man

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Phasic left atrial filling was studied in 20 patients with mitral or aortic valve disease at the time of cardiac catheterisation using an intravascular electromagnetic flow velocity probe placed transseptally in a pulmonary vein. Recordings were made during quiet spontaneous respiration. Pulmonary vein blood velocity showed phasic variations closely following and inversely related to changes in the left atrial pressure. In patients in sinus rhythm with normal atrial pressure, forward flow in systole was biphasic with an early velocity wave resulting from atrial relaxation and a late wave which peaked soon after the nadir of the X pressure descent in the left atrium, coincidental with descent of the atrioventricular ring. Minimum forward velocity in late systole occurred with the peak of the left atrial V wave.

These velocity/pressure events were observed only in hearts in sinus rhythm with pronounced systolic descents in the left atrial pressure trace. A different left atrial filling pattern was seen in abnormal hearts where the X pressure descent was diminished as a result of left ventricular dysfunction, atrial fibrillation, or mitral regurgitation. In these patients, systolic forward flow in the pulmonary veins was delayed and diminished, occurring at the time when atrial pressure was rising.

The findings suggest that in the normal heart, left atrial filling is by atrial suction and mean left atrial pressure is low. In the presence of abnormal left heart function or atrial fibrillation, transmitted pulmonary artery flow fills the left atrium at the haemodynamic cost of a higher left atrial pressure.

Assessment of aortic regurgitation by transcutaneous aortovelography

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Bristol Royal Infirmary

Using the haemotachograph, an ultrasonic Doppler-shift instrument, the instantaneous peak aortic velocity pattern was recorded transcutaneously in 25 normal subjects and 25 patients with aortic regurgitation.

In aortic regurgitation, there was significant retrograde diastolic flow that was not present in normals. The area under the systolic and diastolic waveform was proportional to the forward and backward stroke volume and the ratio between these two areas was used to give an estimate of percentage regurgitation which ranged from 0 to 70 per cent. The peak systolic velocity in patients with more than trivial regurgitation was higher than the range for normals, but there was no correlation between this value and percentage regurgitation.

The degree of aortic regurgitation in the 25 patients was also graded into mild, moderate, and severe, using clinical, echocardiographic, and angiographic criteria where available. Comparison of the aortovelographic percentage regurgitation with this grading gave good agreement in all groups. The percentage regurgitation in the three grades was 0 to 31 per cent, 32 to 41 per cent, and 42 to 70 per cent.

Ten of the patients to date have been catheterised and the percentage regurgitation assessed by comparison of ventricular output determined by single plane cineangiography and Fick cardiac output. A strong correlation has been obtained with the aortovelographic estimate. In the first 6 patients $r = 0 \cdot 92$.

We conclude that transcutaneous aortovelography is a simple, accurate, non-invasive technique for the assessment of aortic regurgitation.

Atypical aortic valve stenosis—a diffuse congenital cardiovascular disease—recognition and surgical management

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In a consecutive series of 77 patients aged 4 to 16 years who had operation for congenital aortic valve stenosis there were 13 in whom the congenital disease was not confined to the aortic valve and open aortic valvotomy is not the ideal treatment.

In this group, the bicuspid or tricuspid aortic valve is cartilaginous, the aortic root is small often with slight supravalve narrowing, left ventricular subvalvar hypertrophy is pronounced with endocardial thickening over the septum, and echocardiograms show the disproportional ventricular septal thickening. Three had a history of failure and cardiomegaly in infancy which responded to medical therapy. Biopsy of the ascending aorta in 9 showed severe 'higgledy piggledy' disorder of the media. After operation, high subvalvar gradients were produced with isoprenaline in 10 despite good relief of the valvar obstruction.

The inevitable valve replacement needed 5 to 20 years after the first valvotomy was difficult owing to the small root and diffuse left ventricular obstruction. We believe that in these patients, who must be identified before the first operation, the correct treatment is complete removal of the aortic root and stenotic valve with reimplantation of the coronary arteries into an adult size homograft, as was first performed in 1965.

In 9 patients the 1- to 11-year follow-up has been good and investigations show relief of obstruction.

Pulmonary vasculature in congenital heart disease

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Different types of congenital heart disease can be regarded as vicarious experiments from which it is possible to derive information about the relation between structure and function in the developing lung. In the pulmonary circulation abnormal haemodynamic conditions modify structure even in utero and after birth rapidly influence the development of the acinar region. Before birth pulmonary and aortic atresia produce different and opposite haemodynamic and structural effects altering the number of intra-acinar arteries formed and the size and wall structure of both pre- and intra-acinar vessels. When the haemodynamic abnormality arises after birth structural changes develop rapidly during the first weeks of life, often leading to the erroneous impression of persistence of fetal muscularity. In young children with ventricular septal defect and pulmonary hypertension an increase in resistance is associated with failure of the intra-acinar pulmonary circulation to develop normally and not with obliterative pulmonary vascular disease. Haemodynamic findings do not have the same structural implications in the immature as in the mature lung. Our findings suggest that in children with congenital heart disease the classical changes of pulmonary vascular disease are superimposed on an incompletely developed pulmonary circulation.

Double inlet right ventricle

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A morphologically right ventrilce receiving both atrioventricular valves is a rare but important anomaly. Described as a variant of single ventricle, others have documented similar cases exhibiting remnants of the left ventricle. We have studied 8 examples of the malformation at necropsy. In all the trabeculated pouch of the left ventricle was identified, to the left of the right ventricle in 7 and to the right in the other. Six were from situs solitus individuals, 2 from situs ambiguous patients. Three hearts, including both the latter, had common atrioventricular valves. In 2 of those, and 3 of the 5 with 2 valves, chords straddled the septum to arise from the trabeculated pouch. The greater part of both atrial orifices, however, drained to the right ventricle. In 3 hearts the pouch was devoid of tension apparatus. In all hearts a posterior septum was identified extending to the crus cordis. Therefore, though double inlet ventricles, these hearts were not primitive ventricles. Surgical corrective procedures would be similar in the two anomalies, but differentiation is important because of the variation in position of the conducting tissues. Clinical diagnosis had been difficult in our cases, but was possible by retrospective study of available angiograms. Morphogenetically, the hearts represent the endpoint of a spectrum characterised by straddling of the mitral valve.

Diagnosis of ventriculoarterial discordance (transposition of great arteries) using contrast echocardiography

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Using the standard left parasternal echocardiographic approach it is not possible definitely to differentiate the aorta from the pulmonary artery in the neonatal period. However, regardless of the relation of the great arteries at their origin from the heart, the arch of the aorta always crosses the bifurcation of the pulmonary artery superiorly and anteriorly. Thus when both great arteries are identified echocardiographically from the suprasternal notch the aorta will always be the proximal great artery. The great artery connected most directly to the systemic venous return can be identified using a peripheral injection of 5 per cent dextrose and recording echocardiographically its passage through the echo beam. Using the suprasternal approach the distal great artery will opacify when the great artery connections are concordant (normal), and when the connections are discordant (transposition) the proximal great artery will opacify. We used this technique retrospectively in 5 cases known to have transposition. Opacification of both great arteries occurred in all 5 cases, because of the bidirectional shunting. In 4, opacification of the aorta was more intense than that of the pulmonary artery. In 1 case with a large ventricular septal defect and free ventricular mixing both great arteries opacified equally. Using this technique we have subsequently accurately predicted the diagnosis in one neonate before catheterisation. We suggest that this technique is a useful diagnostic procedure in ventriculoarterial discordance (transposition) with intact ventricular septum.

Comparison of real-time B-scan and M-scan echocardiography in total anomalous pulmonary venous drainage

C. G. MacArthur and J. Gehrke
Royal Postgraduate Medical School, London

Five children aged from 1 month to 8 years with total anomalous pulmonary venous drainage have been studied before operation by 'Vidoson' real-time B-scanning and in 4 cases also by M-scan echocardiography. The anomalous drainage was supracardiac in 2 children, at cardiac level in another 2, and infradiaphragmatic into the portal vein in 1 infant. In 1 child with the supracardiac variety, there was also transposition of the great arteries.

On M-scan the abnormalities previously described (Paquet and Gutgesell, 1975) were confirmed in 3 cases, but the pulmonary venous chamber could not be identified in the child who also had transposition. In contrast, this chamber behind the left atrium was visualised in all cases on B-scan, and furthermore it was clearly different in the 3 types of anomalous drainage. The features of right ventricular volume overload were present on echocardiograms by both techniques in all cases with isolated total anomalous pulmonary venous drainage.

Postoperative studies were obtained in 1 child. Though the right ventricle was still enlarged, septal motion had become normal. The posterior venous chamber was no longer visible on M-scan, but on B-scan a smaller chamber could still be seen.

This study indicates that B-scan echocardiography is at least as good as the M-scan technique for diagnosing total anomalous pulmonary venous drainage and that it gives added information on the type of drainage involved.

Reference

Paquet, M. and Gutgesell, H. (1975). Echocardiographic features of total anomalous pulmonary venous connection. *Circulation*, **51**, 599-605.

Factors influencing prognosis of patients on pacemakers

W. Ginks, H. Siddons, and A. Leatham
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SW1X 7EZ

Between the years 1960 and 1974, 839 patients were paced for chronic atrioventricular block.

Analysis of survival compared with the general population showed that 169·9 deaths were expected according to standard mortality tables and 288 deaths occurred, giving a ratio of actual to expected deaths of 1·7:1.

As expected, those patients with a history of myocardial infarction or cardiac failure showed a higher than average mortality when paced. Mortality was not influenced if heart block had been established or intermittent, whether the ventricular rate was below or above 40 per minute or whether QRS duration was greater or less than 0·1 s.

Analysis of the age groups paced revealed the most important correlations. Between the ages of 80 and 89 years paced patients could expect to survive as long as others of the same age without heart block. There was, however, a very high mortality ratio of 4·46:1 for 90 patients in the age group 50 to 59 years. The reason for the high mortality ratio was uncertain but it may have been the result of the greater incidence of coronary artery disease in this group, and perhaps, therefore, further investigations with a view to coronary artery surgery should be considered for such patients. Preliminary studies will be discussed.

Relation between posture, pulse pressure, and electrophysiological properties of atrioventricular pathways in patients with paroxysmal supraventricular tachycardias

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In 7 patients with paroxysmal supraventricular tachycardia, measurements of femoral artery pressure during an intracardiac electrophysiological study were repeated at four different angles of head-up tilt (0, 15, 30, 45 degrees), permitting observation of the relation between pulse pressure, posture, and atrioventricular conduction and refractoriness.

Pulse pressure varied most at the onset of rapid fixed rate atrial pacing, the initial fall being greater with the patient tilted. Once the pulse pressure was stable it fell little more if the tilt was increased. Changes in atrioventricular nodal conduction time (AH interval) at the onset of fixed right atrial pacing were not closely related to changes in pulse pressure, but shortened with increasing tilt once pulse pressure was stable.

Cycle length, atrioventricular nodal conduction time, and refractoriness, pulse pressure and posture being interrelated, may all vary during paroxysmal re-entry atrioventricular tachycardia: this relation was studied in 4 patients in whom such attacks could be induced.

Pulse pressure fell most rapidly during the latter part of continuous incremental atrial pacing: the fall was more pronounced at increased degrees of tilt. Both the cycle length at which second degree atrioventricular block occurred and the shortest RR interval during incremental atrial pacing shortened with increased tilt.

These findings help explain the clinical features and mechanisms of paroxysmal supraventricular tachycardias.

Recognition and implications of concealed pre-excitation

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In manifest ventricular pre-excitation both the normal and accessory atrioventricular pathways conduct anterogradely. We have recognised concealed pre-excitation in 21 of 66 cases of paroxysmal re-entry atrioventricular tachycardia, as well as in 6 of 13 with lone atrial fibrillation.

Of 79 patients who underwent intracardiac electrophysiological study, 45 had the Wolff-Parkinson-White syndrome (WPW); 17 had concealed pre-excitation with a normal resting surface electrocardiogram.

Of 11 with a partial atrioventricular nodal bypass, only 6 had the Lown-Ganong-Levine syndrome (LGL), the other 5 showed a normal PR interval. Lone atrial fibrillation occurred in 2 with concealed WPW and in 4 with hidden LGL.

Alternating cycle lengths and either a fixed ventriculoatrial or atrioventricular conduction time during treatment of paroxysmal re-entry atrioventricular tachycardia suggested the presence of an accessory pathway in 18; in 11 of these pre-excitation was otherwise concealed.

Bundle-branch block that developed during paroxysmal re-entry atrioventricular tachycardia and that prolonged its cycle length showed hidden WPW in 4. In 2 with established bundle-branch block and in another with hypertrophic obstructive cardiomyopathy, the resting electrocardiogram obscured the WPW syndrome.

Three with an inverted P wave in lead I during paroxysmal re-entry atrioventricular tachycardia had concealed left-sided accessory pathways. In 4, pre-excitation became apparent after spontaneous atrial arrhythmias.

Knowledge of the presence of an accessory pathway in patients with paroxysmal arrhythmias often assists subsequent investigation, assessment, and management; these observations form a basis for revealing pre-excitation from the electrocardiogram in cases where this is otherwise concealed.

Junctional recovery and conduction times in congenital complete atrioventricular block

J. Camm, A. M. Levy, and R. A. J. Spurrell
St. Bartholomew's Hospital, London EC1; and Medical Centre Hospital, Burlington, Vermont, U.S.A.

Twenty patients with congenital, complete heart block were studied by intracardiac electrography and programmed stimulation. All patients had narrow QRS complexes and supra-Hisian block. HV intervals varied from 20 to 55 ms (mean 39 ± 11). The His depolarisation was validated by His bundle pacing.

Junctional conduction times were measured by isolated His bundle extrasystoles. The junctional conduction times varied from 45 to 120 ms (mean 75 ± 28). In 5 patients the junctional conduction time was significantly ($P < 0{\cdot}01$) reduced after the administration of intravenous atropine (0·3 to 1·0 mg) and increased (NS) by intravenous verapamil (0·1 mg/kg) in 4 patients.

The recovery time of the natural pacemaker after various durations and frequencies of fixed rate His bundle pacing was measured. Maximum recovery time was achieved at frequencies above 100 bpm for durations of 1 minute or more. The maximum recovery time of the natural pacemaker did not correlate with symptoms. It was significantly reduced by atropine ($P < 0{\cdot}001$) and insignificantly reduced by verapamil. The maximum recovery time after atropine correlated with symptoms.

The mean junctional conduction time, prolongation by verapamil and reduction by atropine, suggests a high atrioventricular nodal natural pacemaker. The post-atropine maximum recovery time of the natural pacemaker may determine the need for permanent pacing.

Notices

British Heart Journal, 1977, **39,** 934

International Congress on Prevention of Heart Disease and Cardiac Rehabilitation

An International Congress on Prevention of Heart Disease and Cardiac Rehabilitation will be held in Bombay on 10, 11, 12 September 1978, under the auspices of Society for Prevention of Heart Disease and Rehabilitation.

For details, write to Dr. C. V. Shah, Secretary-General, International Congress on Prevention of Heart Disease and Cardiac Rehabilitation, India House No. 2, Kemp's Corner, Bombay 400 036, India.

Einthoven Symposium on Developments in Electrocardiography 1927-1977

A symposium will be held in the lecture hall of the Laboratory of Physiology, Wassenaarseweg 62, Leiden, Netherlands, on 28 October 1977 in commemoration of Willen Einthoven's death 50 years ago.

Information can be obtained from A. C. Arntzenius, Department of Cardiology, University Hospital Leiden, Rijnsburgerweg 10, Leiden, Netherlands.

Computers in Cardiology

The fourth international conference on Computers in Cardiology will be held from 29 September to 1 October 1977, at the Thoraxcentrum of the Erasmus University in Rotterdam, The Netherlands.

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Verner,I.R., Postgrad.med.J.,1974,*50*,576
Kohli,R.K., and Elwood,C.M., Amer.Fam.Phycn.,1977,*15*,141
Tinker,J.H., and Michenfelder,J.D., Anesthesiology,1976,*45*,No.3,340
Palmer,R.F., and Lasseter,K.C., New Engl.J.Med.,1975,*292*,294

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"Overall, bumetanide showed itself to be a safe and effective diuretic when administered to severely ill patients in a a busy hospital milieu."[5]

Fast Acting

"The rapid absorption from the gastro-intestinal tract is reflected in the brisk diuresis established within the hour."[1]

"Its (Burinex Injection) onset of action is within 10 min."[2]

"Bumetanide is rapidly absorbed from the gut."[3]

The Morning OR Evening diuretic

"The rapid onset and short duration of action of loop diuretics are clearly desirable when a rapid diuresis is indicated, and when given in the evening to patients with chronic heart failure, the short duration of action can ensure a good nights sleep undisturbed by nocturia or breathlessness."[9]

"The use of potent and short-acting diuretics such as bumetanide allow the Physician and patient scope to decide upon the most appropriate time for administration and so reduce major disruptions in the patient's daily routine."[10]

"Patients who go out to work may find Burinex K given in the evening more socially acceptable."[11]

The correct amount of K

"It is known from short-term studies that 1 mg. of bumetanide increases the excretion of potassium by 10-15 mmol daily (Asbury et al, 1972; Olesen et al, 1973; Davies et al, 1974). Two tablets of the combined preparation Burinex K contain 1 mg. of bumetanide and 16 mmol of potassium."[8]

Clinically Effective

"Fourteen patients showed a good diuretic response on bumetanide where previous treatment with frusemide had proved either unsatisfactory or too slow."[5]

"An impressive diminution of the signs of pulmonary oedema was seen in most patients and in some the clearance of alveolar oedema was dramatic."[6]

"Based upon our experience with the use of bumetanide in several hundreds of patients and the detailed studies reported above, it may be concluded that this new diuretic agent is a very useful drug in the treatment of congestive cardiac failure."[7]

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Patients prefer Burinex K

"These results indicate that when long-term diuretic/potassium supplement therapy is required, Burinex K is a more acceptable regimen to the patients than one in which diuretic + Slow K are given separately."[13]

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Burinex K*

Tablets contain 0.5 mg bumetanide with a slow release core of 573 mg (7.7mEq) of potassium chloride.

1. Postgrad. Med. J., 51, 10, (1975)
2. Danish Med. Bull., 21, 63, (1974)
3. Clin. Pharm. Ther., 15, 141, (1974)
4. J. Int. Med. Res., 2, 314, (1974)
5. Brit. J. Clin. Prac., 28, 311, (1974)
6. Brit. J. Clin. Prac., 29, 7, (1975)
7. Postgrad. Med. J., 51, (Suppl. 6), 54, (1975)
8. Brit. J. Clin. Prac. 30, 11-14 (1976)
9. Leading Article, Brit. Med. J., 2, 521, (1975)
10. J. Int. Med. Res., 3, 241, (1975)
11. Postgrad. Med. J., 51, (Suppl. 6), 71, (1975)
12. Acta. Med. Scand., 193, 119, (1973)
13. J. Int. Med. Res., 3, 104, (1975)
14. J. Int. Med. Res., 4, 37-41 (1976)

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October 1977 Vol 39 No 10

British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

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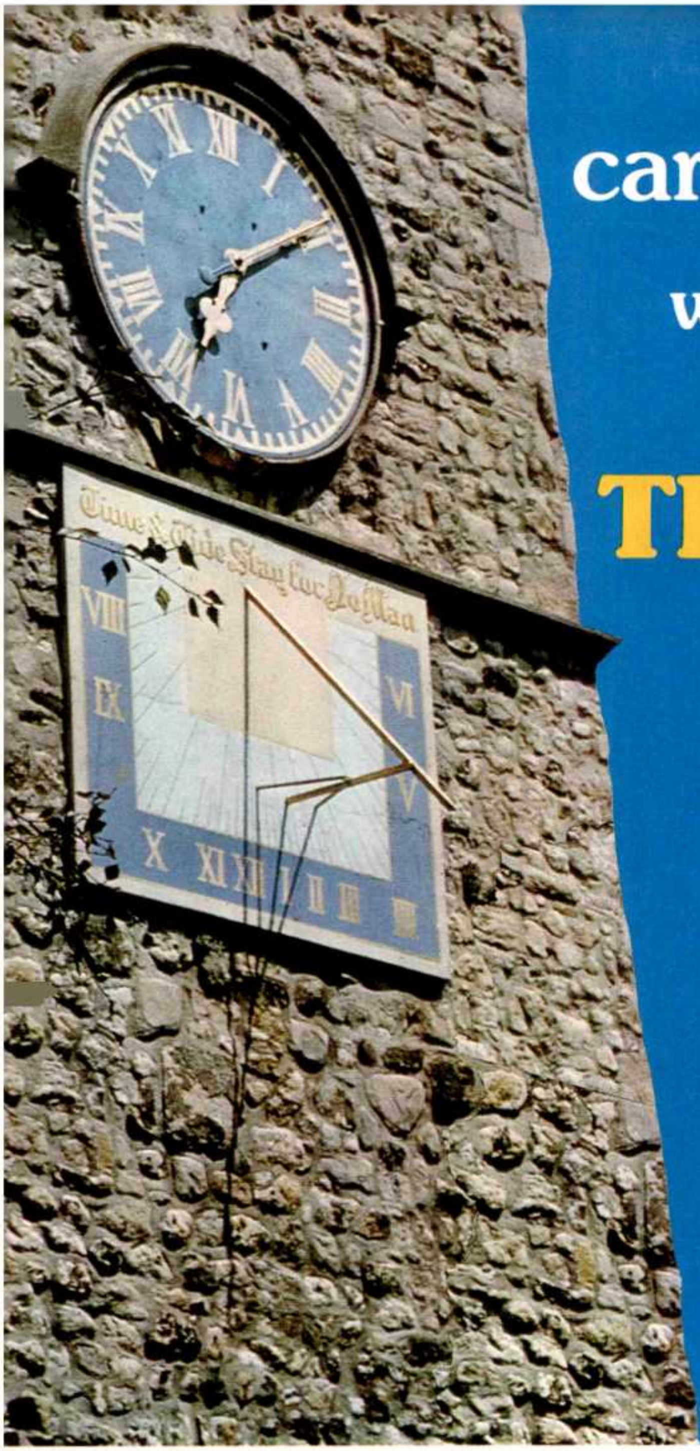

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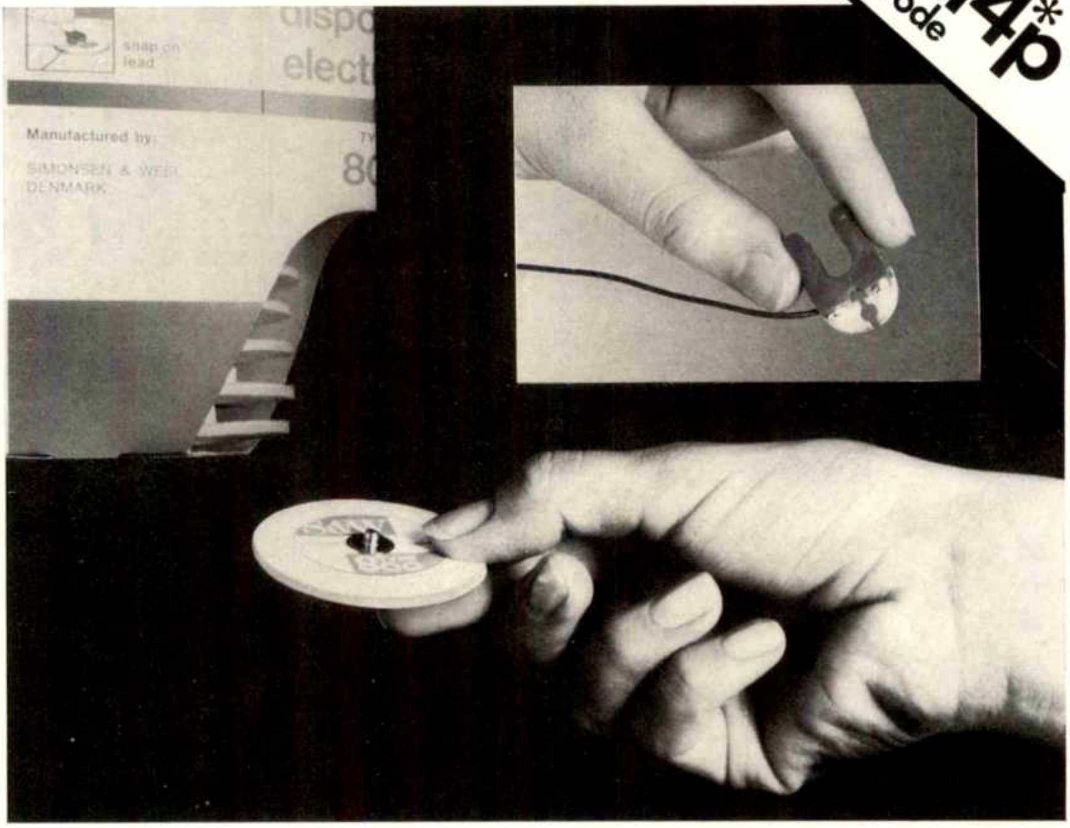

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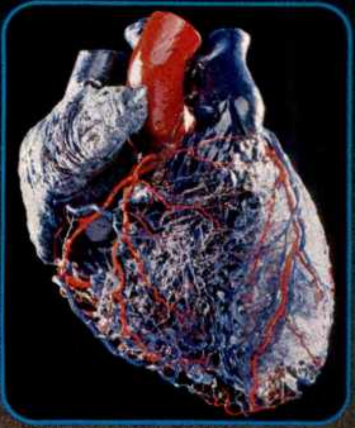

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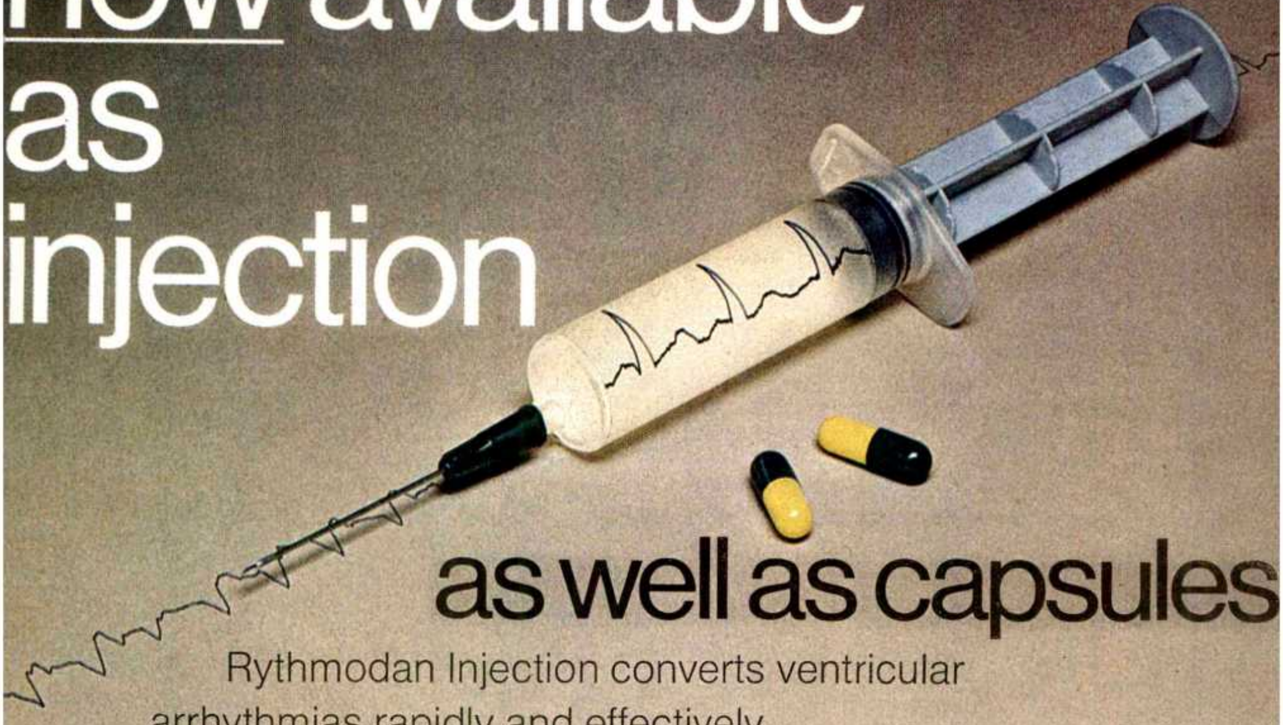

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Edited by Stephen Lock and Heather Windle

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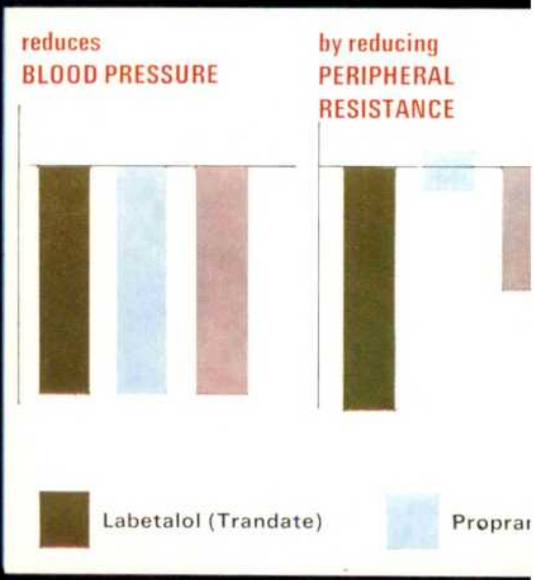

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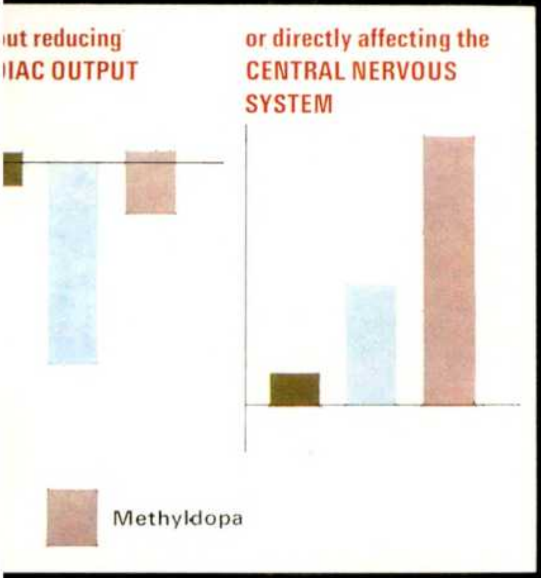

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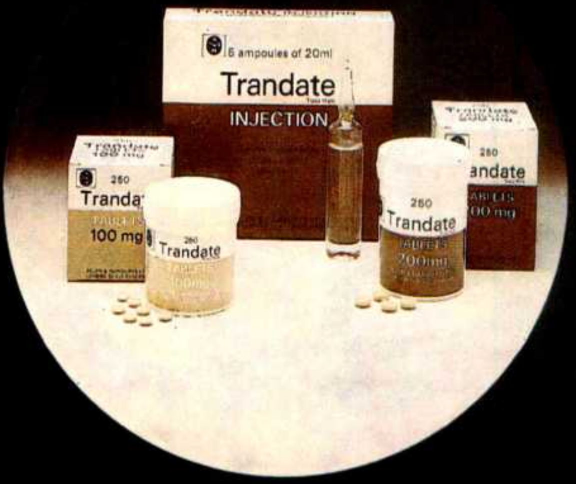

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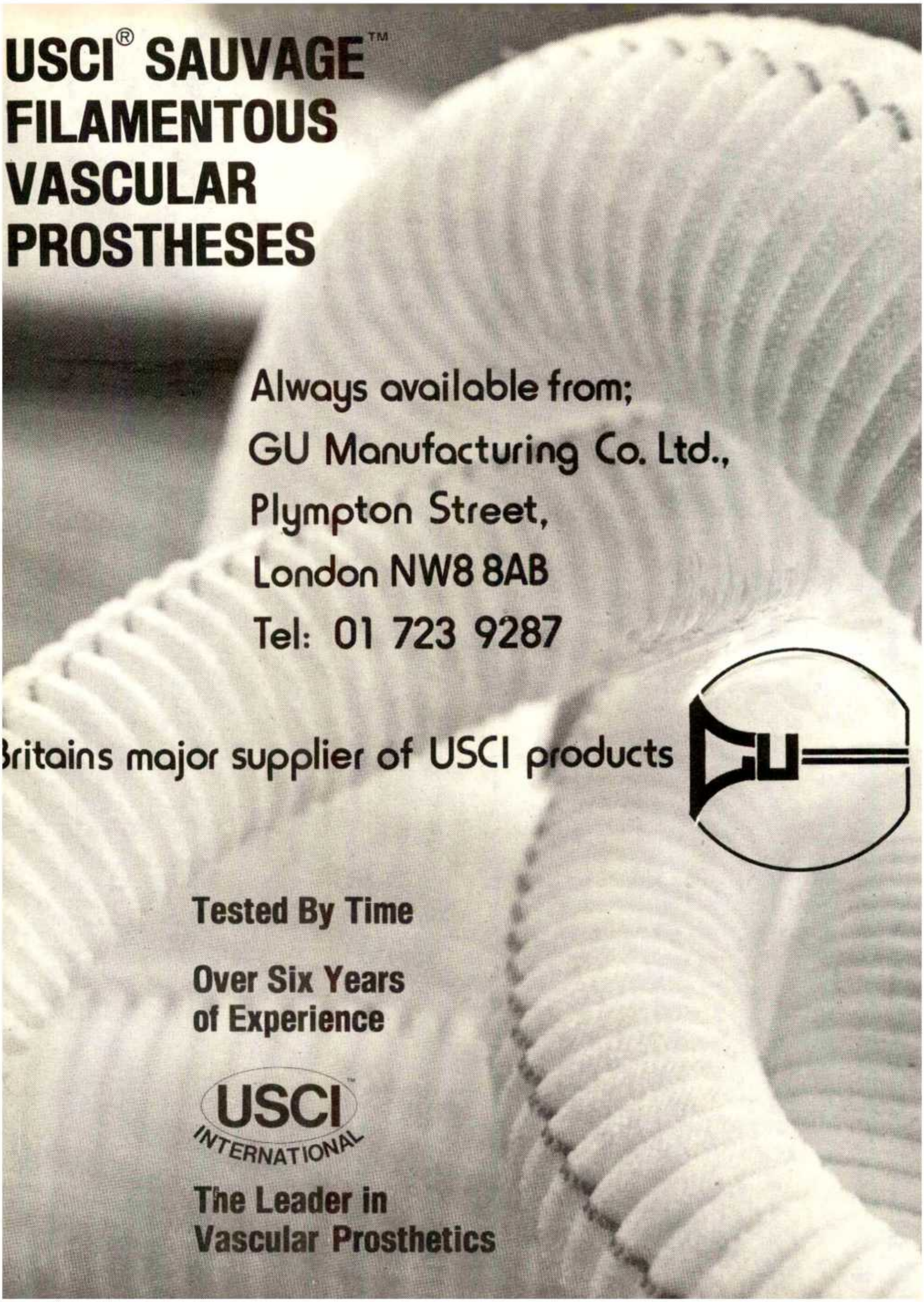

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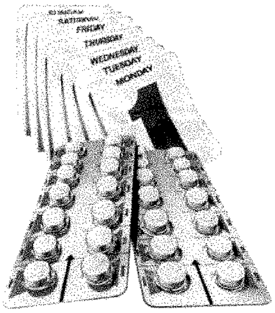

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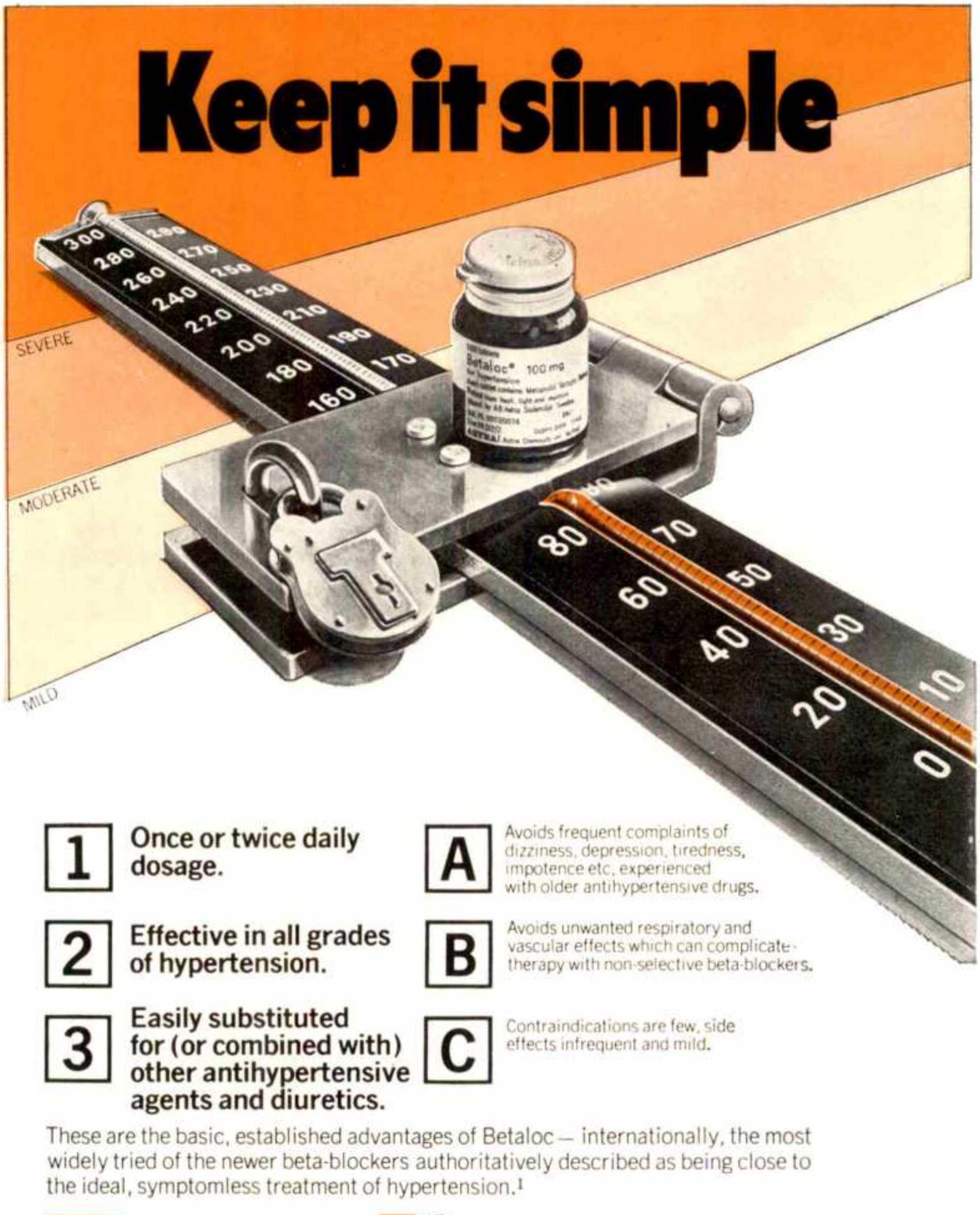

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4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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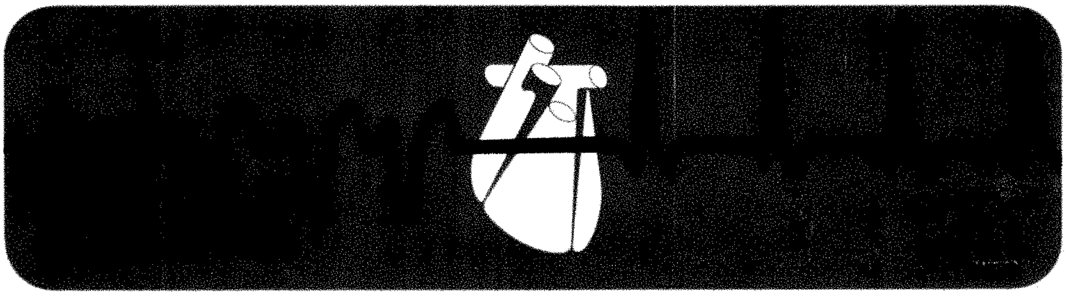

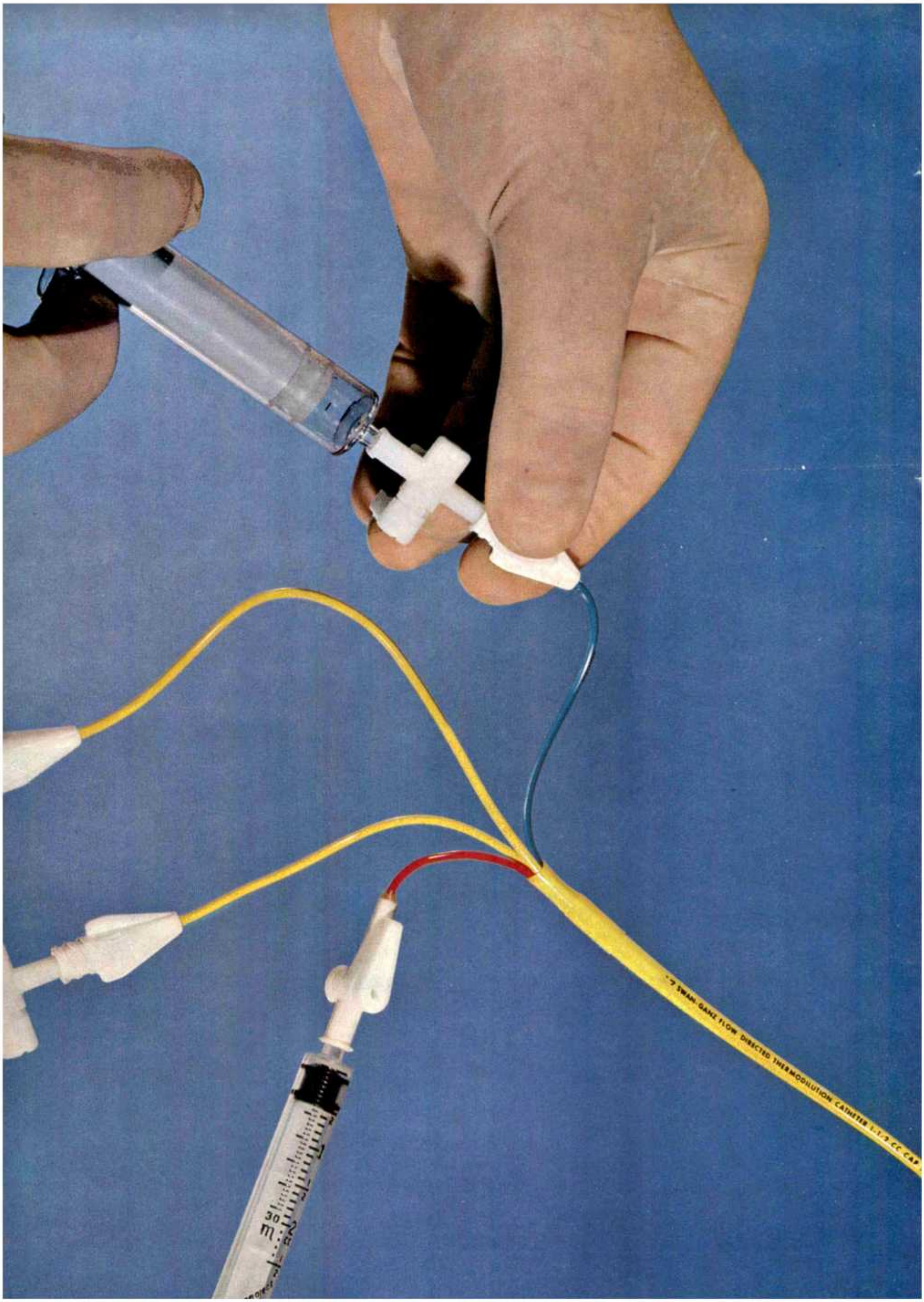
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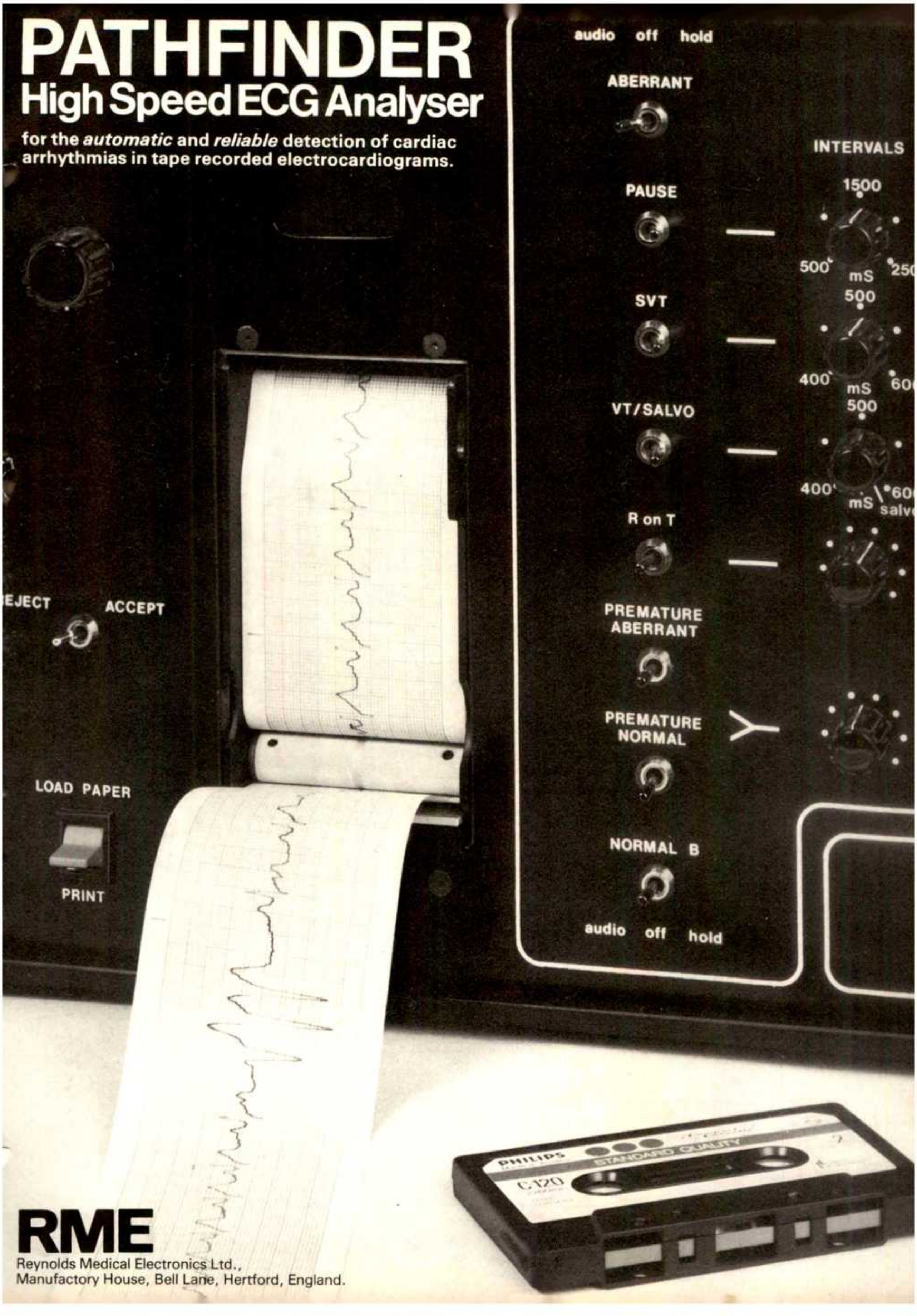

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Verner,I.R., Postgrad.med.J.,1974,*50*,576
Kohli,R.K., and Elwood,C.M., Amer.Fam.Phycn.,1977,*15*,141
Tinker,J.H., and Michenfelder,J.D., Anesthesiology,1976,*45*,No.3,340
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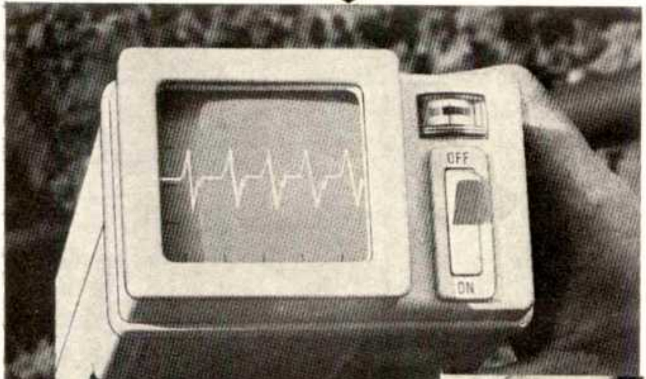

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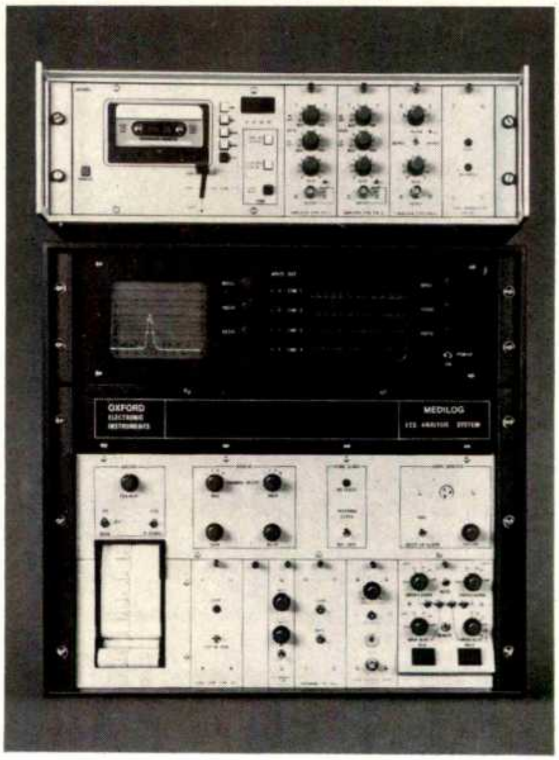

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British Heart Journal, 1977, **39**, 1045-1050

Recognition of rheumatic heart disease[1]

P. R. FLEMING

From Westminster Medical School, London

Although rheumatic carditis was being diagnosed not infrequently during the first third of the 19th century, its firm establishment as a clinical entity is commonly attributed to Bouillaud who published his *Law of Coincidence* of pericarditis and endocarditis with acute rheumatism in 1836. Bouillaud himself certainly believed that he was breaking new ground and anticipated opposition to his statement that, 'This coincidence is the rule and the non-coincidence the exception'. This paper examines whether Bouillaud's claims to priority can be justified or whether the condition was already well known by the time he wrote about it.

James Hope among many others, was certainly aware of the existence of rheumatic heart disease by 1832 and, in 1839 he quoted Bouillaud's views and continued 'He (Bouillaud) . . . inculcates it as a novel doctrine and, to corroborate this opinion, does me the honour of a quotation to show that I was fully acquainted with it. I have not, however, the slightest pretension to originality in this idea; since, at the time when I wrote (1832), there was not a better established doctrine in the London schools'.

By the end of the 18th century the clinical picture of acute articular rheumatism was tolerably well known. Baillou had given an account of its manifestations, on a humoral basis, in 1591 (published posthumously in 1762) and Sydenham recognised the disease as a clinical entity in the 17th century (Keil, 1936). There was, however, probably still some difficulty in separating it from other varieties of acute arthritis and Haygarth wrote in 1805 'The term rheumatism . . . includes a great variety of disorders'.

Parallel with the gradual recognition of rheumatic fever as an entity there were many reports of various forms of heart disease much of which, in retrospect, must have been of rheumatic aetiology though the association was not suspected. Avenzoar had described pericarditis in the 12th century (Garrison, 1929); Benivieni (1507) and Senac (1749) also gave necropsy accounts of this condition. Valve lesions too had been described—by Cowper (1706), Lancisi (1707), Vieussens (1715), and Morgagni (1761).

During the early part of the 18th century the possibility of visceral complications of acute rheumatism was clearly being considered. Boerhaave, Storck and Van Swieten seemed to have some conception of such complications though cardiac involvement was not specified; Cullen, however, while giving a clear account of the articular features, denied the 'recession' of rheumatism into the internal organs (Keil, 1936). The specific association of rheumatism with heart disease was not then suspected though, as Wells (1812) said, Morgagni and Ferriar had noticed the association—apparently as an interesting coincidence.

The recognition of rheumatic carditis began about 1788 when, on the testimony of Baillie (1797) and Wells (1812), David Pitcairn began to point out the association of organic heart disease with rheumatism to his friends and pupils at St. Bartholomew's Hospital. The first edition of Baillie's *Morbid Anatomy* of 1793 contained an accurate description of pericarditis but without reference to rheumatism as a possible cause. In the second edition of 1797 Baillie quoted Pitcairn's views and stated that, 'the causes which produce a morbid growth of the heart are but little known; one of them would seem to be rheumatism attacking this organ'. This seems to be the earliest statement in print that rheumatism could affect the heart.[1] The morbid anatomical diagnosis was apparently made on the basis of pericarditis, often with an effusion with or without cardiac enlargement. Not for many years was the possibility of endocardial disease considered.

At about the same time as Pitcairn was discussing this newly recognised clinical entity with his colleagues in London, a more formal presentation

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[1] Based on the Sydenham Lecture delivered on 19 January 1976 to the Faculty of the History and Philosophy of Medicine and Pharmacy of the Worshipful Society of Apothecaries of London.

Received for publication 13 January 1977

[1] Jarcho (1958) has, however, pointed out that Benjamin Rush, in 1794, quoted a letter from a correspondent in Dublin in which a case of acute rheumatism was described. Abnormalities of the pulse were present and, 'The opinion of some of the physicians was that the heart was affected as a muscle, by the rheumatism, and alternated with the limbs'. Whether these Irish physicians had, directly or indirectly, become acquainted with Pitcairn's teaching or whether this was an independent diagnostic *tour de force* is not known.

of the topic was being given in Gloucestershire. The Gloucestershire Medical Society had been meeting at the Fleece Inn in Rodborough since May 1788 and on 29 July 1789, 'Mr. Jenner favoured the Society with Remarks on a Disease of the Heart following Acute Rheumatism' (Carter, 1896). In compliance with the rules of the society the manuscript of Jenner's paper was presumably handed to the president, Caleb Parry, to be approved for publication. It appears that this paper, together with others, was lost—to Jenner's great distress. Baron (1838) wrote, 'I have often heard him lament the loss of one of them in particular. It contained observations respecting a disease of the heart which frequently comes on during attacks of acute rheumatism . . . Jenner's observations were original'. In 1805 Jenner wrote to Parry, mentioning the original paper and, quoting another case, re-emphasised the importance of the cardiac complications of rheumatism (Keil, 1936).

Thus, towards the end of the eighteenth century, it seems that some physicians in London, the West Country, and Dublin were aware of the possibility that acute rheumatism could affect the heart. From time to time the diagnosis of rheumatic heart disease was being made with varying degrees of certainty. In 1798, Wells (1812), after consultation with Pitcairn, had made this diagnosis. Dundas (1809) had been seeing cases since 1770 and had certainly acquired a clear conception of the condition by the end of the 18th century; if the Dr. Gillan whom he met at the necropsy on one of his cases was Hugh Gillan, this cannot have been later than 1798, the year in which Gillan died (Munk, 1878). Pemberton of St. George's and Marcet of Guy's had also, according to Dundas, seen and recognised cases of rheumatic carditis in the first decade of the 19th century. Rheumatic 'metastasis . . . to the heart or breast' had been mentioned in 1798 by George Fordyce, senior physician at St. Thomas' and, at the same hospital, several cases of rheumatic carditis were seen by Wells between 1800 and 1810. In 1802 Wagstaffe of Southwark, saw a fatal case of rheumatic pericarditis with cardiac enlargement (Wagstaffe, 1803) and Crowfoot of Beccles described another in 1809.

Outside Britain, the earliest reference to cardiac rheumatism seems to have been in a lecture manual published in 1803 by Louis Odier of Geneva. This consists of notes of lectures given to *officiers de santé* in 1799 and 1800 and was reviewed in the *Edinburgh Medical and Surgical Journal* in 1806. Odier had been a pupil of Cullen, whose views have been quoted above, but nevertheless described 'among the symptoms which are apt to supervene on acute rheumatism . . . an affection of the heart'. Wells suggested that Odier was probably 'not unacquainted' with Baillie's description and the appearance of such comments in a lecture manual rather suggests that Odier believed that heart disease was already well recognised as a complication of rheumatism.

Meanwhile, in Bath, the very existence of rheumatic carditis was still being questioned. Haygarth, who had been in that city since 1798, failed to mention cardiac involvement in his book on acute rheumatism published in 1805. In addition, a book on carditis was published in 1808 by John Davis. Davis regarded carditis as a disease *sui generis* and was unclear about the aetiology of the condition. Joint pains were not conspicuous in his accounts and Davis was reluctant to accept the possibility of involvement of the heart, or of other viscera, in acute rheumatism. This is despite the fact that he must have been acquainted with Parry who was called in consultation on one of the cases he described. It was Dr. Sherwen, late of Enfield, who pointed out to Davis the probability that 'all the cases were . . . varieties of acute rheumatism attacking the heart'. The reviewer of Davis's book in the *Annual Medical Register* (1809) was of the opinion that 'the suggestion of Dr. Sherwen is worthy of attention'. In this review there is clear recognition of the clinical entity and the categorical statement that 'the heart seems particularly liable to suffer in rheumatism'.

In London the situation became somewhat clearer in 1808 when David Dundas read a paper on, 'A peculiar disease of the heart' to the Medico-Chirurgical Society (Dundas, 1809); this paper had not escaped the attention of the reviewer of Davis's book and his views were clearly fortified thereby. Dundas, an apothecary practising in Richmond, described 9 cases of rheumatic carditis seen during the previous 36 years. He believed the condition had never been described before and Wells later castigated him gently for failing to quote, at least, Baillie's account of 1797; this is even more surprising as Baillie was present at, and described the findings of, the necropsy of one of Dundas's cases.

The cases described by Dundas seem, in most respects, typical of acute rheumatic carditis. The cardiac illness began after, or occasionally at the same time as, an attack of articular rheumatism. The dominant complaints were praecordial pain, cough, dyspnoea, palpitations, and 'violent pulsations of the carotid arteries'. The condition most commonly affected the young and had a high mortality, most patients dying with features suggesting congestive cardiac failure. At necropsy evidence of old or recent pericarditis was found with cardiac enlargement including, particularly, dilatation of the left ventricle without hypertrophy; the muscle was often soft and friable. Endocardial lesions were rarely mentioned in the early accounts though Dundas comments that in one case 'the valvulae mitrales were edged with a substance of a spongy appearance, perhaps coagulable lymph'.

On the appearance of the paper by Dundas, William Charles Wells very nearly abandoned his project of publishing his cases of rheumatic carditis. He had contemplated publication as early as 1806 as he 'had good reason to believe that it was unknown to many practitioners of medicine in this country'. Further consideration, however, persuaded him that 'even a repetition of what had already been said (by Dundas) might be useful' and on 3 April 1810, he presented his classical paper 'On Rheumatism of the Heart' to the Society for Improving Medical and Chirurgical Knowledge; the paper was published in the *Transactions* of that society in 1812. Space does not permit a detailed review of this admirable paper which is, in all respects, greatly superior to that of Dundas. After a brief, but comprehensive, account of previous publications on the subject, he presented each of his 14 cases individually, some in considerable detail, with accounts of the necropsy findings in the 6 who died. The clinical histories and postmortem appearances were similar to those described more cursorily by Dundas. In one case 'very minute excrescences resembling small warts' were seen on the internal surface of the left atrium; these were, almost certainly, rheumatic vegetations, a feature which had not previously been specificially noted in this connection.

Wells acknowledged the co-operation of several friends and colleagues in the collection of his cases, particularly William Lister of St. Thomas' and Benjamin Brodie of St. George's. His paper seems to have made a considerable impact as, over 20 years later, in evidence to the Select Committee on Medical Education, William MacMichael, who, unlike his colleagues, could find little good to say of Wells, did at least admit, 'There is one paper I do recollect, which is very important, that on the Rheumatism of the Heart' (Keil, 1936). There certainly seems little doubt that, by the second decade of the 19th century, many physicians were well aware that cardiac involvement could occur in acute rheumatism and that the manifestations of that involvement included pericarditis and disease of the heart muscle. Of rheumatic endocarditis, leading to valvular deformities, very little or nothing was known. Nor does there seem to have been any certainty concerning the frequency with which carditis supervened in acute rheumatism.

During the next two decades knowledge of the existence of acute rheumatic carditis spread widely in Britain and elsewhere, though there were still dissenting voices, among them F. J. Kreysig who wrote a commentary on a German translation by J. L. Choulant of Wells's paper; in Kreysig's opinion Wells's cases were examples of 'gouty heart' (Keil, 1936). The failure of Laennec and Bertin to comment on rheumatism of the heart was even more noteworthy (Brown, 1828). The high, and apparently increasing, incidence of this complication of rheumatic fever gradually became apparent; still more gradually was it realised that the endocardium was very commonly affected and that the long-term sequelae of chronic rheumatic heart disease with valvular lesions frequently dominated the natural history of the disease.

Between 1812 and 1818 knowledge of rheumatic carditis was consolidated. Individual cases, with recovery, were reported by Russell from Birmingham and by Penkivil from Plymouth in 1814. In 1815 Mathey reported 5 cases from Geneva with necropsy reports in 2 in a paper which was reviewed, later that year, in the *London Medical and Physical Journal;* the reviewer commented that no advance had been made on the account of Dundas 6 years earlier. In 1816 an early American account came from James Jackson of Harvard who commented that affection of the heart in rheumatism 'is neither new nor very rare' and, in the same year, John Armstrong touched briefly on rheumatic carditis in a more general discussion on fevers. Also in 1816 Charles Scudamore published a monograph on gout and rheumatism and, after describing a typical case of acute rheumatic carditis, made the following rather unhelpful comment: 'I should rather be disposed to consider the general rheumatism of the constitution to be a predisposing cause of this disease of the heart, than to pronounce it rheumatism of the organ'—a 'risk factor' in modern parlance. In 1817 a London correspondent of the *Edinburgh Medical and Surgical Journal* discussed current views on rheumatic heart disease and pointed out, perhaps for the first time, that, 'the supervening affection of the heart does not always kill during the rheumatism; it frequently remains as a chronic disorder for many months, *or a year or two*'.[1] This phase of consolidation was completed in 1818 by James Johnson who reviewed all that had previously been written about cardiac rheumatism in a work in which were implicit the epidemic constitutions of Hippocrates and Sydenham. Thus, referring to rheumatic metastasis to the heart and writing in the year before the Peterloo massacre, Johnson commented that, 'this is a subject of only modern observation' and 'in a turbulent era . . . certain erratic inflammations, as those of gout, rheumatism, erysipelas, etc., may fall more frequently on an organ preternaturally deranged, than at other periods'. To the previously recorded cases Johnson added several others reported to him by his naval colleagues and emphasised the increasing importance of the condition as follows: 'there are reasonable grounds of belief that the influence of the disease has lately increased, is still increasing, and ought to be diligently watched'.

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[1] My italics.

Until the introduction of mediate auscultation (Laennec, 1819) the clinical diagnosis of carditis in acute rheumatism depended, perforce, on symptoms and signs which were largely non-specific. Inevitably many cases with less severe degrees of cardiac involvement must have been missed and the true frequency of carditis cannot have been appreciated. Nevertheless, among the increasingly numerous publications written on the subject (Reeder, 1821; Armstrong, 1823; Chisholm, 1824; Peyron, 1826; Hawkins, 1827) several emphasised the great frequency with which the heart was affected. The writer of a review article in the *London Medical Repository* for 1823 said 'The translation of this affection (rheumatism) to the heart has become of so frequent occurrence, that it is no longer looked on as an unusual circumstance'. Thomas Cox, in 1825, described the 'numerous cases' of rheumatic heart disease he had seen in and around Guy's Hospital. Robert Adams, in Dublin, had seen 'many cases' by 1827 and commented, 'It is scarcely necessary to dwell upon this subject, as rheumatism of the heart, since Doctor Baillie introduced the subject to notice, has been much spoken of.' Samuel Broughton, surgeon to the Life Guards, presented yet another case in 1827, though, as he said, the condition was 'now well known and understood' and Joseph Brown of Sunderland was so impressed with the importance of rheumatism in the aetiology of heart disease that he wrote, in 1828, 'when called to a case of affection of the heart, my first enquiry is whether the patient has been subject to rheumatism'. Only Scudamore (1827) of the more important writers on the subject, regarded carditis as a rare complication of rheumatism; indeed he adduced the rarity of carditis compared with the frequency of rheumatism as evidence in favour of his reiterated thesis that rheumatism was a predisposing cause of heart disease rather than a 'metastasis'.

In none of the publications hitherto discussed did endocarditis receive any significant emphasis and it was not until 10 years after the introduction of mediate auscultation that cases of rheumatism were, at last, being described in which cardiac murmurs were heard during life. Among five cases from St. George's Hospital described in 1829 and 1830 in the *Medico-Chirurgical Review*, a *bruit de scie* (saw sound) was heard in one and, in two cases from the London Hospital described in 1830 in the *London Medical and Physical Journal*, a 'bellows-sound' was heard; in one of these right ventricular and left atrial hypertrophy and tight mitral stenosis with ossification of the valve were found at necropsy. Particularly in the writings of James Hope (1832) one finds, as in so many other respects, an account of rheumatic heart disease which could almost have appeared in a modern textbook. Among the causes of pericarditis 'far above all', in his view, was rheumatism. Even more impressive is his account of the aetiology of chronic valve disease. He described the 'Exciting causes of valvular induration' as follows: 'These are, first, such as overstrain the valves by increasing the force of the circulation; namely violent efforts, hypertrophy, increased action of the heart from nervous, febrile or inflammatory excitement: secondly inflammation of the internal membrane of the heart, resulting from carditis . . . especially rheumatic'.

The importance of auscultation was further emphasised, implicitly, in a short paper by Roots of St. Thomas' Hospital (1836) in which he described a case in which a pericardial friction rub was heard, but 'there was not the slightest bellows-sound'; he inferred from this that no endocarditis was present. Whether or not this was a correct inference is irrelevant; the important fact is that Roots realised that both pericarditis and endocarditis could be present in rheumatic carditis and that each could be diagnosed separately.

Thus it would seem, perhaps, that Hope was correct in stating that Bouillaud's 'novel doctrine' was already established in the London schools by 1836. Hope and Roots, however, were leaders of the profession; Hope 'opened wide the portals of the heart'[1] and Roots raised the reputation of St. Thomas' Hospital 'to a point which has not been equalled at any other period in the history of that institution' (*Lancet*, 1861). It is not possible to say with certainty how widely diffused was the knowledge that rheumatic carditis is a pancarditis. However advanced was the practice of some London physicians, Bouillaud's publication of 1836 was the first to state that, in patients suffering, or even convalescent, from rheumatic fever, examination by percussion and auscultation would, more often than not, reveal evidence of cardiac enlargement and valvular disease. It is also, perhaps, not without significance that, in his third edition of 1839, Hope inverted his original order of 'Exciting causes of valvular induration', placing rheumatism above 'violent efforts' and other causes of 'overstrain' of the valves. Hope and his colleagues were certainly aware of the clinical pictures of acute rheumatic carditis and chronic rheumatic heart disease, but Bouillaud was the first to describe them clearly and in detail. From the time of his publication, there was no longer any dispute about the relation between acute articular rheumatism and inflammation of the pericardium, myocardium, and endocardium with consequent valvular deformities. After 40 years of debate, the clinical picture was complete and there seems no reason to disagree with Ackerknecht's (1967) pithy comment that 'only Bouillaud made it stick'.

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[1] From a elegy on Hope by C.L.M. (perhaps Charles Lewis Meryon), quoted by East (1958).

References

Ackerknecht, E H. (1967). *Medicine at the Paris Hospital, 1794–1848.* The Johns Hopkins Press, Baltimore.

Adams, R. (1827). Cases of diseases of the heart accompanied by pathological observations. *Dublin Hospital Reports,* **4,** 353.

Armstrong, A. (1823). Case of acute rheumatism translated to the heart. *London Medical and Physical Journal,* **49,** 215.

Armstrong, J. (1816). *Practical Illustrations of Typhus and Other Febrile Diseases,* pp. 206 and 208. Longman, London.

Baillie, M. (1793). *The Morbid Anatomy of Some of the Most Important Parts of the Human Body,* J. Johnson and G. Nicol, London.

Baillie, M. (1797). *The Morbid Anatomy of Some of the Most Important Parts of the Human Body,* 2nd ed. J. Johnson and G. Nicol, London.

Baillou, G. (1762). *Liber de Rheumatismo.* Geneva. (Cited by Major, 1945.)

Baron, J. (1838). *The Life of Edward Jenner, M.D., LL.D., F.R.S.,* Vol. 1, p. 45. Colburn, London.

Benivieni, A. (1507). *De abditis nonnullis ac mirandis morborum et sanationum causis.* Florence. (Cited by Long, E. R. (1928). *A History of Pathology.* Williams and Wilkins, Baltimore.)

Bouillaud, J. (1836). *Nouvelles Recherches sur le Rhumatisme Articulaire Aigu en Général, et Spécialement sur la Loi de Coincidence de la Pericardite et de la Endocardite avec cette Maladie.* Baillière, Paris. Translated by Kitchen, J. (1837). Haswell, Philadelphia.

Broughton, S. D. (1827). Case of pericarditis, connected with acute rheumatism, successfully treated. *London Medical and Physical Journal,* n.s. **3,** 508.

Brown, J. (1828). *Medical Essays, on Fever, Inflammation, Rheumatism, Diseases of the Heart, etc.,* p. 166. Longman, London.

Carter, A. H. (1896). Records of an old medical society. Some unpublished manuscripts of Edward Jenner. *British Medical Journal,* **1,** 1296–1298.

Chisholm, R. (1824). A report of the medical cases treated at the Kent and Canterbury Hospital, from the 1st of January to the 30th June, 1824. *London Medical Repository,* n.s. **2.**

Cowper, W. (1706). On ossifications or petrifactions in the coats of arteries, particularly in the valves of the great artery. *Philosophical Transactions of the Royal Society,* **24,** 1970–1977. (Cited by Major, 1945.)

Cox, T. (1825). Observations on acute rheumatism and its metastasis to the heart, etc. London, 1824. Reviewed in *Medico-Chirurgical Review,* **2,** 428–432.

Crowfoot, W. H. (1809). Two cases of carditis. *Edinburgh Medical and Surgical Journal,* **5,** 298–300.

Davis, J. F. (1808). *An Inquiry into the Symptoms and Treatment of Carditis or the Inflammation of the Heart Illustrated by Cases and Dissections.* Longman, London.

Davis, J. F. (1809). Review of. *Annual Medical Register,* **1,** 112.

Dundas, D. (1809). An account of a peculiar disease of the heart. *Medico-Chirurgical Transactions,* **1,** 37–46.

East, T. (1958). *The Story of Heart Disease. The Fitzpatrick Lectures for 1956 and 1957.* Dawson, London.

Edinburgh Medical and Surgical Journal (1817). Extracts from a letter from a physician in London, **13,** 249–253.

Fordyce, G. (1798). *A Third Dissertation on Fever,* Part 1. J. Johnson, London.

Garrison, F. H. (1929). *An Introduction to the History of Medicine,* 4th ed., p. 132. Saunders, Philadelphia.

Hawkins, F. (1827). Goulstonian Lectures for 1826. Reviewed in *London Medical and Physical Journal,* **57,** 260.

Haygarth, J. (1805). *Clinical History of Diseases, Part 1. Clinical History of the Acute Rheumatism or Rheumatic Fever.* Cadell and Davies, London.

Hope, J. (1832). *A Treatise on the Diseases of the Heart and Great Vessels.* Kidd, London.

Hope, J. (1839). *A Treatise on the Diseases of the Heart and Great Vessels,* 3rd ed. J. Churchill, London.

Jackson, J. (1816). On rheumatism in the heart, eyes, etc. *London Medical and Physical Journal,* **36,** 200. (Reprinted from *New England Journal of Medicine.*)

Jarcho, S. (1958). Rheumatic carditis: Bouillaud and some unknown Irish precursors. *American Journal of Cardiology,* **1,** 514–516.

Johnson, J. (1818). *The Influence of the Atmosphere, More Especially the Atmosphere of the British Isles, on the Health and Functions of the Human Frame.* Underwood, London.

Keil, H. (1936). Dr. William Charles Wells and his contribution to the study of rheumatic fever. *Bulletin of the Institute of the History of Medicine,* **4,** 789–816.

Laennec, R. T. H. (1819). *De l'Auscultation Médiate.* J. A. Brosson and J. S. Chaudé, Paris.

Lancet (1861). Obituary of H. S. Roots, **1,** 279–280.

Lancisi, G. M. (1707). De subitaneis mortibus libri duo. J. F. Buagni, Rome. (Cited by Major, 1945.)

London Medical and Physical Journal (1830). Hospital Reports: London Hospital, **63,** 322.

London Medical Repository (1823). Historical sketch of the progress of medicine for the first six months of 1823. **20,** 26.

Major, R. H. (1945). *Classic Descriptions of Disease,* 3rd ed. Thomas, Springfield, Illinois.

Mathey, A. (1815). Memoir on rheumatism of the heart. Reviewed in *London Medical and Physical Journal,* **34,** 84.

Medico-Chirurgical Review (1829). Hospital Reports: St. George's Hospital. Diseases of the heart. **11,** 556–563.

Medico-Chirurgical Review (1830). Hospital Reports: St. George's Hospital. On pericarditis. **13,** 183–190.

Morgagni, G. B. (1761). *De sedibus, et causis morborum.* Translated by B. Alexander (1769). A. Millar and T. Cadell, London.

Munk, W. (1878). *The Roll of the Royal College of Physicians of London,* Vol II. London.

Odier, L. (1803). Manuel de médecine pratique, ou sommaire d'un cours gratuit donné l'an vii et l'an viii de la Republique Francaise aux officiers de Santé du département du Léman. Reviewed in *Edinburgh Medical and Surgical Journal,* 1806, **2,** 446–453.

Penkivil, J. (1814). Case of rheumatism of the heart. *Edinburgh Medical and Surgical Journal,* **10,** 355–357.

Peyron, M. (1826). Case of rheumatism of the heart, treated by acupuncture. *London Medical and Physical Journal,* **56,** 379. (Reprinted from *Revue Médicale.*)

Reeder, H. (1821). A practical treatise on the inflammatory, organic and sympathetic diseases of the heart. Reviewed in *London Medical and Physical Journal,* **46,** 569.

Roots, H. S. (1836). Acute pericarditis supervening in rheumatism. *St. Thomas's Hospital Reports*, **1**, 397.

Russell, J. (1814). Case of rheumatism of the heart successfully treated. *Edinburgh Medical and Surgical Journal*, **10**, 18–21.

Scudamore, C. (1816). *A Treatise on the Nature and Cure of Gout Comprehending a General View of a Morbid State of the Digestive Organs; and of Regimen; with Observations on Rheumatism.* Longman, London.

Scudamore, C. (1827). *A Treatise on the Nature and Cure of Rheumatism with Observations on Rheumatic Neuralgia, and on Spasmodic Neuralgia or Tic Douloureux.* Longman, London.

Senac, J. B. (1749). *Traité de la Structure du Coeur, de son Action et de ses Maladies.* Vincent, Paris. (Cited by Willius, F. A., and Keys, T. E. (1961). *Classics of Cardiology,* Vol. 1. Dover, New York.)

Vieussens, R. (1715). *Traité Nouveau de la Structure et des Causes du Mouvement Naturel du Coeur.* Guillemette, Toulouse. (Cited by Major, 1945.)

Wagstaffe, M. F. (1803). A case of thoracic adhesions. *Medical and Physical Journal*, **9**, 359.

Wells, W. C. (1812). On rheumatism of the heart. *Transactions of the Society for Improving Medical and Chirurgical Knowledge*, **3**, 373–424.

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Thyrotoxicosis and lactate-producing angina pectoris with normal coronary arteries

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Three patients with thyrotoxicosis are described, in whom the presenting symptom was severe cardiac pain at rest or on effort and who were admitted to hospital with suspected or proven myocardial infarction. All patients were studied by selective coronary arteriography and left ventriculography after thyroid function tests which confirmed thyrotoxicosis. There was no demonstrable disease of the major coronary arteries in any of the patients, yet myocardial infarction and left ventricular aneurysm were shown to be present in 1, and there was definite electrocardiographic evidence of ischaemia in all 3. In addition, under stress the myocardium of all 3 patients produced lactate. It is recommended that thyrotoxicosis be seriously considered in the differential diagnosis of cardiac pain, particularly in younger women. The cause of the pain seems related to the cellular effects of thyrotoxicosis on the myocardium and current views of these effects are summarised. Of the 3 patients, 1 died suddenly 6 months after becoming euthyroid, indicating that the disease may not be as benign as expected. A guarded prognosis and continued medical follow-up are recommended when thyrotoxicosis presents with angina pectoris even when normal coronary arteries have been demonstrated.

Coronary arterial disease remains the single most important cause of cardiac pain. Angina pectoris may be mimicked, however, by disease processes affecting the myocardium not a result of diffuse or obstructive lesions of the coronary arteries. Having recently investigated 3 patients admitted to hospital with myocardial infarction or unstable angina pectoris, in all of whom thyrotoxicosis was present, we wish to draw attention to thyrotoxicosis as a cause of cardiac pain, particularly in younger adult women. Selective coronary arteriography excluded epicardial coronary arterial disease as a cause but myocardial lactate production was elicited by the stress of provoked tachycardia and/or afterload elevation, strongly suggesting myocardial cellular hypoxia as the origin of their presenting symptoms.

Methods of study

Cinecoronary arteriography was performed by the Judkins (1967) technique and multiple oblique projections obtained after selective injections in each coronary ostium. Simultaneous blood samples from the coronary sinus and a systemic artery were obtained in duplicate in each of the following states: (i) control; (ii) right ventricular pacing at a rate of 130 a minute for 3 minutes; (iii) right ventricular pacing at a rate of 150 a minute; (iv) control; (v) phenylephrine infusion (20 mg/500 ml) intravenously at rates sufficient to raise the systolic blood pressure by 30 to 40 mmHg for 3 minutes; (vi) ventricular pacing at a rate of 130 a minute while phenylephrine infusion was continued for 3 minutes; (vii) final control. In 1 patient (case 2) ventricular pacing only was performed.

Plasma lactate was analysed by the technique of Vaughan and Galloway (1964). Lactate extraction (production), expressed as a percentage, was calculated from the formula:

$$[(A-V)\times A^{-1}\times 100]\%$$

where: A and V represent arterial and coronary sinus blood plasma concentration of lactate, respectively.

Normal lactate extraction is considered to be more than 10 per cent. Lactate extraction of less than 10 per cent or any degree of lactate production (negative ratio) is considered to be biochemical evidence of myocardial ischaemia.

Selective left ventriculography in two planes was also obtained and the films analysed for abnormalities of ventricular function and contraction. Left ventricular and aortic pressures were recorded.

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Patients studied

CASE 1

A 37-year-old woman was admitted to the coronary care unit with a diagnosis of acute myocardial infarction. Typical angina pectoris associated with shortness of breath and diaphoresis occurred before admission to hospital. Initially in sinus rhythm, atrial fibrillation supervened but the ventricular rate was difficult to control with digoxin. Serial electrocardiograms indicated anteroseptal infarction with persistent elevation of ST segments, suggesting ventricular aneurysm (Fig. 1). There were no obvious clinical signs of thyrotoxicosis and a goitre was not felt. Thyroid function tests were nevertheless grossly abnormal with a free thyroxine index (FTI) of 18·0 μg/100 ml (232 nmol/l) and a total thyroxine level (TT_4) of 20·2 μg/100 ml (260 nmol/l). Upper normal limits in our laboratory for these tests are FTI 9·3 μg/100 ml (120 nmol/l) and TT_4 9·4 μg T_4/100 ml (121 nmol/l). Despite bedrest and controlling the ventricular rate with a combination of digoxin 0·5 mg/day and propranolol 160 mg/day, she continued to have angina pectoris on effort. Cardiac catheterisation studies as previously outlined were performed 6 weeks after acute infarction, at a time when the thyrotoxicosis was brought under medical control. Left and right coronary arteries showed no lesions or irregularities of their major branches (Fig. 2C, D). The left ventricular pressure was 160/21 mmHg. Biplane left ventricular cineangiocardiography in the anteroposterior and lateral projections showed moderate hypertrophy of the left ventricle with pronounced hypokinesis of the anterior wall and a large apical aneurysm (Fig. 2A, B). The remainder of the ventricle contracted well and there was no mitral regurgitation. After left ventriculography, left ventricular pressure rose to 160/40 mmHg. Immediately after the anatomical study, a myocardial lactate investigation was performed. Though lactate was not produced during the control state, pacing and phenylephrine drug infusion alone and in combination resulted in an abnormal response with lactate production (Fig. 3 and Table). The patient did not experience any angina pectoris during this study. She has continued well since discharge from hospital and is now euthyroid.

CASE 2

A 40-year-old woman was admitted to the coronary care unit with suspected myocardial infarction because of severe typical angina pectoris which was recurrent and prolonged even at rest. The electrocardiogram indicated a pattern suggesting anterior infarction with added transient ST segment depression during episodes of pain (Fig. 4), but there was no evolution of this pattern nor were sequential serum enzyme levels (CK and LDH) diagnostic of infarction. The thyroid gland was palpably enlarged but there were no clinical signs of thyrotoxicosis. The FTI value was 26·9 μg/100 ml (346 nmol/l), the TT_4 was 19·9 μg/100 ml (256 nmol/l), and a thyroid scan showed a 24-hour uptake of 51 per cent.

After the thyrotoxicosis had been treated cardiac catheterisation showed a resting left ventricular pressure of 160/20 mmHg. The left ventriculogram in the anteroposterior and lateral projections was normal and selective coronary arteriography showed normal major epicardial vessels and their branches. A myocardial lactate study indicated that no lactate was produced during control, but there was an abnormal lactate response after the heart rate was

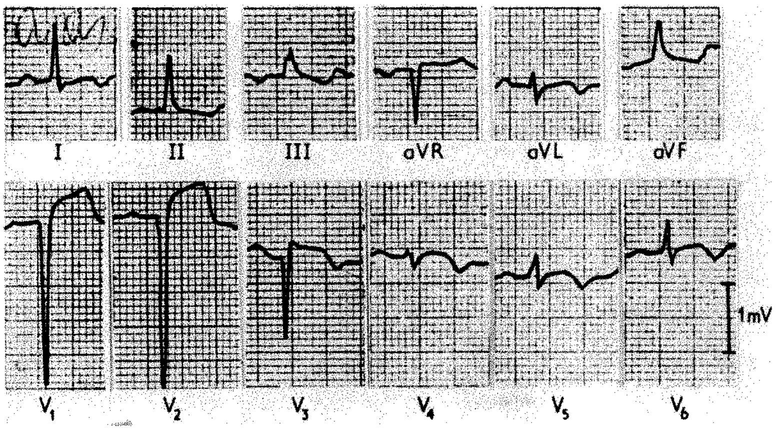

Fig. 1 *Electrocardiogram, case 1. Note the pattern of anterior transmural myocardial infarction. The ST segment elevation persisted, suggesting ventricular aneurysm.*

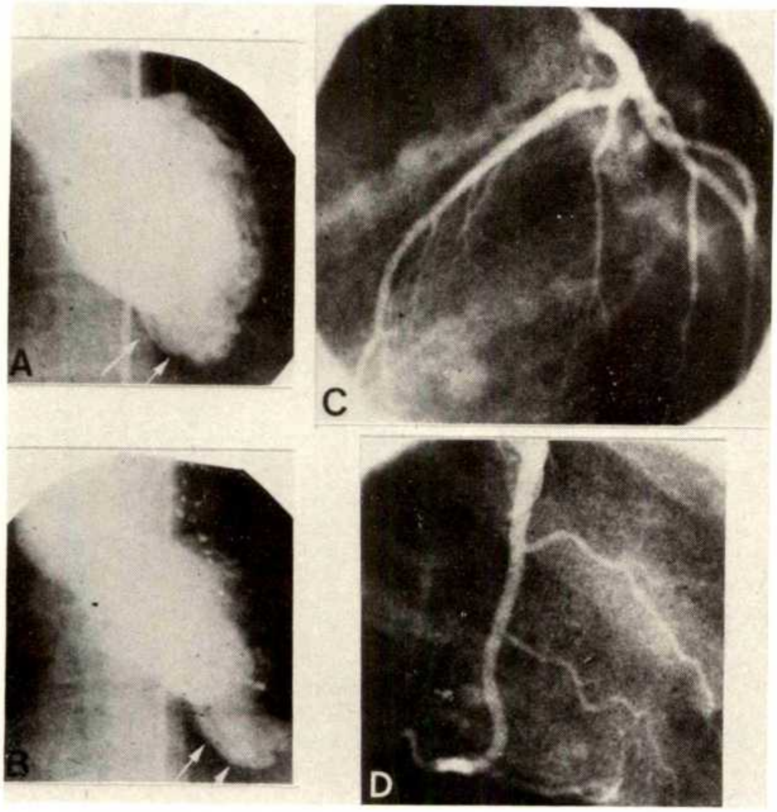

Fig. 2 *Left ventriculogram (A, B) and selective coronary arteriogram (C, D), case 1. (A) diastolic frame, anteroposterior projection; (B) systolic frame, anteroposterior projection; (C) left coronary artery, left anterior oblique projection; (D) right coronary artery, right anterior oblique projection.*
In A and B arrows point to the left ventricular aneurysm. Normal left and right coronary arteries are shown in C and D.

raised to 150 beats a minute by right ventricular pacing (Table).

The thyrotoxicosis was treated continuously with propylthiouracil 200 mg 3 times daily and, in addition, she was given propranolol to a total of 160 mg each day. Subsequently, radioactive iodine was given, after blocking the thyroid gland. Initially, she did well, but 6 months later suddenly collapsed in the street and died. There was no necropsy.

Fig. 3 *Myocardial lactate study, case 1. Figures represent the product of heart rate and mean arterial blood pressure (see Table and text). There is lactate production when the myocardium is stressed by increasing the heart rate to 130/minute by right ventricular pacing (P), by increasing the afterload using an intravenous infusion of phenylephrine (PH), or by a combination of these 2 measures (P and PH). During control measures (C) there is no lactate production. A control value was also obtained after pacing alone (Table) but has been omitted in this figure for the sake of clarity.* →

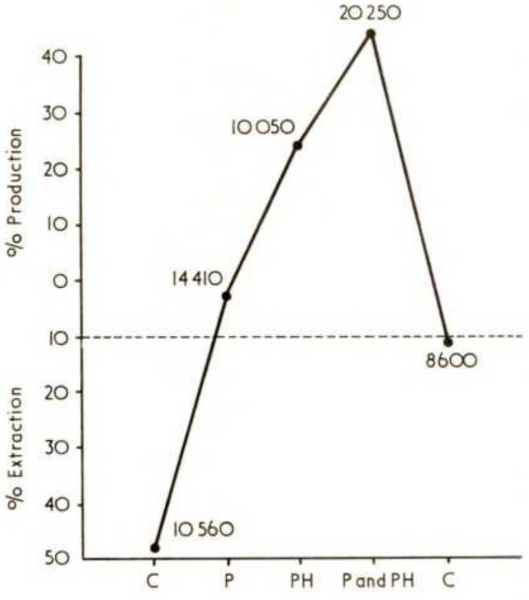

Table *Results of myocardial lactate study: lactate production is always abnormal*

Status	*Case 1*			*Case 2*			*Case 3*		
	*$HR \times \overline{BP}$**	*Lactate %*		*$HR \times \overline{BP}$**	*Lactate %*		*$HR \times \overline{BP}$**	*Lactate %*	
		Extraction	*Production*		*Extraction*	*Production*		*Extraction*	*Production*
Control 1	10 560	48	0	14 400	15	0	11 250	29	0
Pacing†									
Rate 130	14 410	0	3	23 460	19	0	—	—	—
Rate 150	18 600	0	1	29 750	0	28	13 502	13	0
Control 2	11 250	14	0	—	—	—	11 760	48	0
Phenylephrine	10 050	0	24	—	—	—	10 080	43	0
Phenylephrine and pacing†									
Rate 130	20 250	0	44	—	—	—	14 144	0	7
Control 3	8 600	11	0	—	—	—	10 656	13	0

*$HR \times \overline{BP}$, heart rate per minute × mean arterial blood pressure, mmHg.
†Pacing, right ventricular endocardial pacing.

CASE 3

A 24-year-old woman was admitted for investigation with a history, starting 1 year previously, of angina pectoris occurring on effort and more recently at rest. In addition, extrasystoles had been noted and there was nervousness. There had been no loss of weight. The thyroid gland was moderately enlarged. There were no abnormal features on examination of the cardiovascular system, nor was the heart enlarged on the chest *x*-ray film. The resting electrocardiogram showed minor nonspecific ST-T wave changes. Thyroid function tests revealed a TT_4 of 11·1 µg/100 ml (143 nmol/l) and an FTI of 15·1 µg/100 ml (194 nmol/l) and the thyroid scan confirmed enlargement of the gland and revealed a 24-hour uptake of 76 per cent.

Cardiac catheterisation showed normal left and right sided pressures and a normal resting cardiac output. Biplane left ventriculography did not reveal any abnormalities. A lactate pacing study was performed, and showed no lactate production during control or with ventricular pacing to a rate of 150 a minute. During ventricular pacing and a simultaneous intravenous infusion of phenylephrine, however, an abnormal response occurred with the production of 7 per cent lactate (Table).

Her thyrotoxicosis was brought under control by medical management and she has continued well since.

Discussion

Conditions causing cardiac pain typical of angina pectoris but not resulting from coronary arterial disease include cardiomyopathy (both obstructive and congestive), aortic valve disease (stenosis and regurgitation), and any form of severe left or right ventricular hypertrophy, including severe pulmonary hypertension. More recently, prolapse of the mitral valve has been recognised as a cause of cardiac pain as have both coronary arterial spasm and 'coronary steal' syndromes. The investigations in the 3 patients presented in this paper show that thyrotoxicosis can affect the myocardium. Under stress and in the absence of any coronary arterial obstruction an abnormal lactate response, with production rather than extraction, occurred suggesting myocardial hypoxia as the reason for the cardiac pain

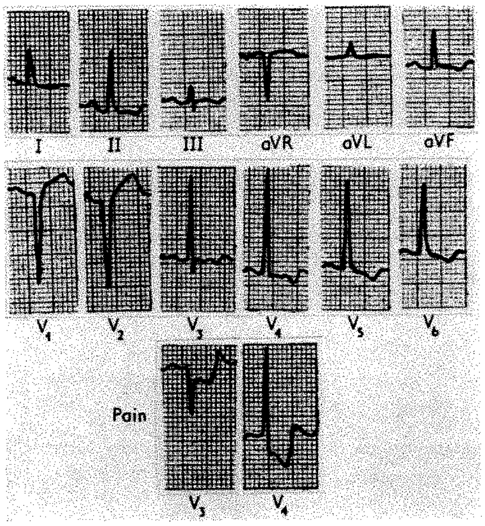

Fig. 4 *Electrocardiogram, case 2. ST segment depression with inverted T in many leads, QS pattern V1 to 2. During an episode of typical cardiac pain occurring at rest, further ST segment depression is recorded in leads V3 and 4.*

and other dramatic clinical abnormalities noted in all 3 patients.

In the presence of ischaemia resulting from coronary arterial disease abnormal myocardial metabolism is well recognised (Magee and Smith, 1935). Both during control and under stress, a normal myocardium consumes lactate in proportion to the arterial lactate concentration. An abnormally low lactate extraction or actual myocardial lactate production occurs in many patients with obstructive lesions of the coronary vessels indicating a change from aerobic to glycolytic metabolic pathways within the myocardial cells as a manifestation of deficient oxygen delivery to the myocardium.

That thyrotoxicosis causes important changes in the cardiovascular system has been known for many years and the evidence of a hyperkinetic circulation is often sought when considering its diagnosis. Whether thyrotoxicosis produces heart disease has been a matter of much debate (Willius *et al.*, 1923; Lahy and Hamilton, 1924; Hurxthal, 1928; Magee and Smith, 1935; Friedberg and Sohval, 1937; Likoff and Levine, 1943; Griswold and Keating, 1949; Cookson, 1959). Summers and Surtees (1961) undertook a careful cardiovascular assessment of 200 unselected patients with thyrotoxicosis to determine the relation between the overactive thyroid gland and heart disease. They found that 30 per cent of the patients had a cardiac abnormality. The older the patient, the greater was the likelihood of cardiac disease being present. Those with definite ischaemic heart disease had the worst prognosis. Symons *et al.* (1971) reported 8 patients age 51 to 68 years who were observed from one to seven years and in whom a persistently raised protein-bound iodine indicated possible thyrotoxicosis which later became established. All 8 patients had evidence of cardiac disease, including rheumatic and non-rheumatic heart disease, and systemic hypertension, and 1 patient had myocardial ischaemia. The remaining 3 patients had paroxysmal or established atrial fibrillation. Cardiac catheterisation or coronary arteriography were not performed. Burstein *et al.* (1960) studied an unselected series of 384 thyrotoxic patients of whom 15 developed signs and symptoms of acute coronary insufficiency or myocardial infarction during the active stage of thyrotoxicosis. In 7, the diagnosis of myocardial infarction was confirmed. It is noteworthy that in this series the proportion of men to women with infarction was 2·3:1, lower than usual and at least 2 of the patients were less than 40 years old. These authors concluded that the association of myocardial infarction and thyrotoxicosis resulted from the effects of the thyrotoxic state on coronary atherosclerosis which was already present. It is, however, important to note that in this study, too, no anatomical details of the coronary arteries of any of the affected patients were available.

In contrast, Duchosal and Henny (1941) reported a patient with thyrotoxicosis and angina pectoris who died shortly after thyroid surgery, and at necropsy the coronary arteries were normal. Similarly, Somerville and Levine (1950), in a study of 24 patients presenting with angina pectoris and thyrotoxicosis, reported that, in one, treatment of the thyrotoxicosis resulted in complete freedom from angina pectoris over the next 17 years of follow-up, suggesting that some process other than coronary arteriosclerosis was responsible for the angina pectoris.

Another effect of thyrotoxicosis on cardiac function has been documented by Campus *et al.* (1975) as heart block, which occurred in 2 patients, 1 of whom had had Adams-Stokes attacks. Both patients reverted to normal conduction when they became euthyroid.

In 1 of our 3 patients (case 1) an electrocardiographic pattern of acute infarction was associated with persistent elevation of the ST segment suggesting a ventricular aneurysm and this was confirmed by selective left ventriculography. No obstructive lesions were present in the epicardial coronary vessels on selective coronary arteriography but she was undoubtedly thyrotoxic as documented by the appropriate tests of thyroid function. That myocardial infarction may occur in patients with angiographically proven patent coronary vessels has been well documented (Likoff *et al.*, 1962; Dear *et al.*, 1971; Glancy *et al.*, 1971). Recently, Eliot *et al.* (1974) performed necropsy studies in 10 patients who died with a typical clinical picture of acute myocardial infarction but in whom there was either none or only minimal coronary atherosclerosis, and suggested that the frequency of infarction without morphological evidence of acute occlusion and without the existence of severe coronary disease might be as high as 7 per cent. There was no mention of the thyroid state of their patients. It is perhaps important to note that atrial fibrillation was present in our patient and that the possibility exists that acute myocardial infarction leading subsequently to the development of a ventricular aneurysm was caused by coronary embolisation from a left atrial thrombus and that the coronary embolus subsequently recanalised leaving no trace on selective coronary arteriography.

The pathophysiology of the cardiac manifestations of hyperthyroidism has been reviewed by DeGroot (1972), DeGroot and Stanbury (1975), and by Levey (1975). An important manifestation is increased adrenergic activity which accounts for many of the classical symptoms of thyrotoxicosis as well as the known circulatory changes. Whether the adrenergic effects are secondary to an increased sensitivity to circulating catecholamine or to an actual increase in catecholamine at the receptor site has not yet been determined (Harrison, 1964; Waldstein, 1966; Levey, 1971), though it now seems likely that in the presence of thyrotoxicosis there remains normal sensitivity to circulating catecholamine. Thus, Wurtman *et al.* (1963) showed there was an increased concentration of free adrenaline and noradrenaline available for interaction with myocardial beta receptors though others have found an actual lowering of the concentration of circulating catecholamines in hypothyroidism (Christensen, 1972; Stoffer *et al.*, 1973).

The physiological effects of excess thyroid hormone are well known but the basic mechanism of reaction of the thyroid hormone on the heart less so. It has been suggested (DeGroot, 1972) that one or more of the following may occur: (1) myocardial changes are secondary to an increased demand for a higher cardiac output resulting from the increased oxygen utilisation in the thyrotoxic state; (2) changes are a result of direct thyroxine action on mitochondrial high phosphate bond synthesis; (3) changes are a result of thyroxine induced increased synthesis of macromolecules of the cell and in the mitochondrion; (4) thyroxine acts by altering myocardial adenyl-cyclase; (5) the observed response is the result of an increased myocardial sensitivity to catecholamines.

Buccino *et al.* (1967) were able to show that thyroid hormone increased the speed of shortening of contractile elements without altering the total force production in an experimental animal model and that the positive inotropic response to noradrenaline varied inversely with the level of the thyroid hormone. Very similar changes were found by Gold and associates (1970) in skeletal muscle. Administration of thyroxine produces myocardial hypertrophy and a dramatic increase in the number of mitochondria (Zaimis *et al.*, 1969), but whether this is a result of the primary effect of the hormone or a secondary mitochondrial response to high energy phosphate utilisation is not yet known (Hoch, 1966). More recently, attention has been directed to the stimulatory effect of thyroxine on adenyl-cyclase as an important mechanism of the myocardial effects of thyrotoxicosis (Levey and Epstein, 1969). It is indeed possible that the augmented myocardial contractility produced by the thyroid hormone or by catecholamines could be mediated by cyclic-AMP (Epstein *et al.*, 1970). One could, therefore, suggest a hypothetical biochemical chain linking adrenaline, adenyl-cyclase, cyclic-AMP, and calcium ion to explain the positive inotropic effects of thyrotoxicosis. Even so, it is important to remember that hypothyroid animals have been reported to have normal amounts of myocardial adenyl-cyclase (Sobel *et al.*, 1969), that myocardial adenyl-cyclase sensitivity to adrenaline is not increased in thyrotoxicosis, and that myocardial cyclic-AMP levels are not usually found to be augmented in thyrotoxic animal preparations (McNeill *et al.*, 1969).

A further possible explanation of the effects of thyrotoxicosis on the heart was suggested by Challoner (1968), namely that the thyroid hormone may act by uncoupling oxidative phosphorylation in the myocardium.

Trying to summarise the evidence for the effects of thyroid hormone on the heart, DeGroot (1972) suggested that it caused both direct and indirect actions on cardiac function, probably mediated through changes in macromolecular synthesis in the nucleus or cytoplasm of the myocardial cell, rather than by a direct effect of the hormone on mitochondrial oxidative phosphorylation. Nevertheless, Ismail-Beigi and Edelman (1970) have already shown that there is an alteration of membrane ATP-ase after administering thyroxine and it is clear that much additional work needs to be done before the actual mechanism is known.

Whatever the basic mechanism is, the 3 patients presented in this paper show that thyrotoxicosis may, on occasion, be associated with typical angina pectoris and even the symptoms and electrocardiographic changes of impending or actual myocardial infarction. In 1 of the 3 patients, myocardial infarction did occur and was associated with left ventricular aneurysm. None of the 3 patients showed any evidence of coronary atherosclerosis, but in all, the myocardium produced lactate under stress, either during cardiac pacing or when the afterload was also raised by phenylephrine. On return to the control heart rate and blood pressure, myocardial lactate was no longer produced. Thus, there is clear evidence in all 3 patients that myocardial hypoxia could be produced by increasing the myocardial oxygen demand, indicating that there was difficulty in oxygen delivery, transport, and utilisation by the myocardial cell in the presence of thyrotoxicosis and in the absence of coronary atherosclerosis.

In 2 of the patients, the clinical picture was greatly improved after treatment of the thyrotoxicosis and with the establishment of a euthyroid state. Despite being euthyroid, however, 1 of the 3 patients (case 2) died suddenly and unexpectedly, indicating that the condition is not always benign.

On the basis of the 3 patients presented the following recommendations seem appropriate. Thyrotoxicosis should always be excluded when angina pectoris occurs, particularly in younger female patients. If thyrotoxicosis is present, a guarded prognosis should be given and continued medical follow-up advised after treatment even when no abnormalities of the coronary arteries have been shown by selective coronary arteriography.

References

Buccino, R. A., Spann, J. F., Jr., Pool, P. E., Sonnenblick, E. H., and Braunwald, E. (1967). Influence of the thyroid state on the intrinsic contactile properties and energy stores of the myocardium. *Journal of Clinical Investigation*, **46**, 1669–1682.

Burstein, J., Lamberg, B-A., and Erämaa, E. (1960). Myocardial infarction in thyrotoxicosis. *Acta Medica Scandinavica*, **166**, 379–393.

Campus, S., Rappelli, A., Malvasi, A., and Satta, A. (1975). Heart block and hyperthyroidism. *Archives of Internal Medicine*, **135**, 1091–1095.

Challoner, D. R. (1968). Evidence for uncoupled respiration in thyrotoxic and epinephrine-stimulated myocardium. *American Journal of Physiology*, **214**, 365–369.

Christensen, N. J. (1972). Increased levels of plasma noradrenaline in hypothyroidism. *Journal of Clinical Endocrinology and Metabolism*, **35**, 359–363.

Cookson, H. (1959). The thyroid and the heart. *British Medical Journal*, **1**, 254–259.

Dear, H. D., Russell, R. O., Jones, W. B., and Reeves, T. J. (1971). Myocardial infarction in the absence of coronary occlusion. *American Journal of Cardiology*, **28**, 718–721.

DeGroot, L. J. (1972). Thyroid and the heart. *Mayo Clinic Proceedings*, **47**, 864–871.

DeGroot, L. J., and Stanbury, J. B. (1975). *The Thyroid and its Diseases*, 4th ed. John Wiley, New York.

Duchosal, P. W., and Henny, G. (1941). Angine de poitrine et hyperthyroidisme. *Cardiologia*, **5**, 372–387.

Eliot, R. S., Baroldi, G., and Leone, A. (1974). Necropsy studies in myocardial infarction with minimal or no coronary luminal reduction due to atherosclerosis. *Circulation*, **49**, 1127–1131.

Epstein, S. E., Skelton, C. L., Levey, G. S., and Entman, M. (1970). Adenyl-cyclase and myocardial contractility. *Annals of Internal Medicine*, **72**, 561–578.

Friedberg, C. H., and Sohval, A. R. (1937). The occurrence and the pathogenesis of cardiac hypertrophy in Graves' disease. *American Heart Journal*, **13**, 599–618.

Glancy, D. L., Marcus, M. L., and Epstein, S. E. (1971). Myocardial infarction in young women with normal coronary arteriograms. *Circulation*, **44**, 495–502.

Gold, H. K., Spann, J. F., Jr., and Braunwald, E. (1970). Effect of alterations in the thyroid state on the intrinsic contractile properties of isolated rat skeletal muscle. *Journal of Clinical Investigation*, **49**, 849–854.

Griswold, D., and Keating, J. H., Jr. (1949). Cardiac dysfunction in hyperthyroidism: a study of 810 cases. *American Heart Journal*, **38**, 813–822.

Harrison, T. S. (1964). Adrenal medullary and thyroid relationships. *Physiological Reviews*, **44**, 161–185.

Hoch, F. L. (1966). Rapid effects of a subcalorigenic dose of L-thyroxine on mitochondria. *Journal of Biological Chemistry*, **241**, 524–525.

Hurxthal, L. M. (1928). Heart failure and hyperthyroidism. *American Heart Journal*, **4**, 103–108.

Ismail-Beigi, F., and Edelman, I. S. (1970). Mechanism o thyroid calorigenesis: role of active sodium transport. *Proceedings of the National Academy of Sciences of the United States of America*, **67**, 1071–1078.

Judkins, M. P. (1967). Selective coronary arteriography. Part I. A percutaneous transfemoral technic. *Radiology*, **89**, 815–824.

Lahy, F. H., and Hamilton, B. E. (1924). Thyrocardiacs: their diagnostic difficulties: their surgical treatment. *Surgery, Gynecology and Obstetrics*, **39**, 10–14.

Levey, G. S. (1971). Catecholamine sensitivity, thyroid hormone and the heart. *American Journal of Medicine*, **50**, 413–420.

Levey, G. S. (1975). The heart and hyperthyroidism. Use of beta-adrenergic blocking drugs. *Medical Clinics of North America*, **59**, 1193–1201.

Levey, G. S., and Epstein, S. E. (1969). Myocardial adenyl cyclase: activation by thyroid hormones and evidence for two adenyl cyclase systems. *Journal of Clinical Investigation*, **48**, 1663–1669.

Likoff, W. B., and Levine, S. A. (1943). Thyrotoxicosis as the sole cause of heart failure. *American Journal of the Medical Sciences*, **206**, 425–434.

Likoff, W., Segal, B., and Dreifus, L. (1962). Myocardial infarction patterns in young subjects with normal coronary arteriograms. *Circulation*, **26**, 373–378.

McNeill, J. H., Muschek, L. D., and Brody, T. M. (1969). The effect of tri-iodothyronine on cyclic AMP, phosphorylase, and adenyl cyclase in rat heart. *Canadian Journal of Physiology and Pharmacology*, **47**, 913–916.

Magee, H. R., and Smith, H. L. (1935). Auricular fibrillation in hyperthyroidism. The influence of age. *American Journal of the Medical Sciences*, **189**, 683–690.

Sobel, B. E., Dempsey, P. J., and Cooper, T. (1969). Normal myocardial adenyl cyclase activity in hyperthyroid cats. *Proceedings of the Society for Experimental Biology and Medicine*, **132**, 6–9.

Somerville, W., and Levine, S. A. (1950). Angina pectoris and thyrotoxicosis. *British Heart Journal*, **12**, 245–257.

Stoffer, S. S., Jiang, N-S., Gorman, C. A., and Pikler, G. M. (1973). Plasma catecholamines in hypothyroidism and hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism*, **36**, 587–589.

Summers, V. K., and Surtees, S. J. (1961). Thyrotoxicosis and heart disease. *Acta Medica Scandinavica*, **169**, 661–671.

Symons, C., Richardson, P. J., and Wood, J. B. (1971). Unusual presentation of thyrocardiac disease. *Lancet*, **2**, 1163–1167.

Vaughan, C. W., and Galloway, R. E. (1964). A convenient deproteinizing procedure in the enzymatic determination of lactate and pyruvate in whole blood (abstract). *Alabama Journal of Medical Sciences*, **1**, 104–107.

Waldstein, S. S. (1966). Thyroid-catecholamine interrelations. *Annual Review of Medicine*, **17**, 123–132.

Willius, F. A., Boothby, W. M., and Wilson, L. B. (1923). The heart in exophthalmic goiter and adenoma with hyperthyroidism. *Medical Clinics of North America*, **7**, 189–219.

Wurtman, R. J., Kopin, I. J., and Axelrod, J. (1963). Thyroid function and the cardiac disposition of catecholamines. *Endrocrinology*, **73**, 63–74.

Zaimis, E., Papadaki, L., Ash, A. S. F., Larbi, E., Kakari, S., Matthew, M., and Paradelis, A. (1969). Cardiovascular effects of thyroxine. *Cardiovascular Research*, **3**, 118–133.

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Effect of verapamil studied by programmed electrical stimulation of the heart in patients with paroxysmal re-entrant supraventricular tachycardia

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Atrioventricular (AV) conduction, ventriculoatrial (VA) conduction, and the mechanism of tachycardia, were studied by programmed electrical stimulation before and after the administration of verapamil, in 10 patients with paroxysmal re-entrant supraventricular tachycardia. In 7 patients the tachycardia circuit was confined to the AV node. In 3 patients an accessory pathway conducting only in the ventriculoatrial direction was used during tachycardia. When administered intravenously during tachycardia, verapamil terminated the arrhythmia in 9 patients. Verapamil lengthened the effective and the functional refractory period of the AV node and the AV nodal transmission time in all patients in whom this could be studied. As a result of these changes, it was not possible to initiate tachycardia in 3 patients. The width of the zone of atrial premature beats able to initiate tachycardia (the tachycardia zone) narrowed in 5 patients, and increased in 2 patients. In 6 of these 7 patients the tachycardia zone shifted to longer premature beat intervals. Verapamil resulted in slowing of the heart rate during tachycardia. Apart from slowing in heart rate during tachycardia and termination of tachycardia after intravenous verapamil, the 3 patients with an accessory pathway showed no beneficial effect of verapamil on the mechanism of initiation of tachycardia. Five patients were restudied after 2 to 3 weeks of oral administration of verapamil. Though less, effects were similar to those obtained after intravenous administration.

Several authors have reported on the beneficial effect of verapamil in patients suffering from supraventricular tachycardia (Bender *et al.*, 1966; Bender, 1967; Schamroth, 1971; Schamroth *et al.*, 1972; Krikler and Spurrell, 1974; Härtel and Hartikainen, 1976). To study the mechanism of this effect, the drug was given to 10 patients in whom supraventricular tachycardias could reproducibly be initiated and terminated by programmed electrical stimulation of the heart.

Material and methods

Ten patients were studied (Table 1). All suffered from recurrent attacks of electrocardiographically documented supraventricular tachycardia. During sinus rhythm and tachycardia 9 patients showed a normal QRS, and the other a complete right bundle-branch block configuration. None of the patients showed electrocardiographic evidence of the Wolff-Parkinson-White syndrome. After obtaining informed consent, 4 catheters were introduced into the femoral veins using the Seldinger technique. Two bipolar catheters were positioned high on the lateral wall of the right atrium. One was used for stimulation, the other for recording an intra-atrial electrogram. A tripolar catheter was placed in the region of the bundle of His to record a His bundle electrogram. The fourth (bipolar) catheter was positioned in the apex of the right ventricle and used for ventricular stimulation.

In five patients a left atrial electrogram was recorded by advancing a fifth catheter into the coronary sinus or (through a patent foramen ovale) into the left atrium.

Using the single test stimulus method during right atrial stimulation, the functional and effective refractory periods of the AV node and the effective refractory period of the atrium were measured, and

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the zone of premature beat intervals resulting in atrial echoes or sustained tachycardia determined. Thereafter, using the single test stimulus method, the right ventricle was paced up to its effective refractory period. The refractory period and VA conduction times were measured. Both atrium and ventricle were paced at rates just above the spontaneous sinus rate.

Using criteria previously described (Wellens and Durrer, 1975), 3 patients (Tables 1 and 2, cases 1 to 3) were found to use an accessory AV pathway in the VA direction during tachycardia. In the remaining patients the tachycardia circuit was confined to the AV node. After these measurements and with the patient in tachycardia verapamil (10 mg) was given directly into the right atrium through one of the catheters over a 4-minute period. Within 10 minutes after completion of the drug infusion the same stimulation programme was repeated using identical basic cycle lengths and test stimulus intervals. In 5 patients the stimulation procedure was repeated 2 to 3 weeks later, after they had taken oral verapamil (80 mg 3 times daily) in the interim. Care was taken to use the same basic driving rate and to place the stimulating and recording electrodes as nearly as possible in the same positions during the first and second catheterisations to minimise the effect of varied approaches to the AV node on AV nodal function (Amat *et al.*, 1974; Batsford *et al.*, 1974). All data obtained during the stimulation studies were recorded on tape (Ampex FR 1300) and were directly recorded on an 8-channel Elema Mingograf recorder. Leads I, II, III, V1, V6, the intracavitary right atrial lead, a left atrial lead if available, and the His bundle lead were recorded simultaneously. For recording the His bundle electrogram an Elema EMT 12 was used. Statistical analyses were performed using the paired t test.

The effective refractory period of the AV node was defined as the longest A_1-A_2 interval failing to conduct through the AV node. The functional refractory period of the AV node was defined as the shortest attainable H_1-H_2 interval. Since it was not consistently possible to determine which part of the VA conduction pathway became refractory during ventricular pacing, using the single test stimulus method, no values will be given for the effective

Table 1 *Effects of verapamil on AV conduction*

Case No.	*Sex*	*Age (y)*	*Acc P*	*BCL (ms)*	*AH basic (ms)*				*ERP_{AVN} (ms)*				*FRP_{AVN} (ms)*			
					Before V	*After V*	*Change*	*Oral V*	*Before V*	*After V*	*Change*	*Oral V*	*Before V*	*After V*	*Change*	*Oral V*
1	M	26	+	600	60	90	+30	—	< 220	260	—	—	400	440	+40	—
2	M	48	+	600	80	100	+20	100	< 230	< 200	—	< 200	360	390	+30	360
3	F	64	+	500	90	100	+10	—	< 200	240	—	—	350	370	+20	—
4	M	27	0	600	130	190	+60	180	260	430	170	< 290	350	380	+30	380
5	M	59	0	500	110	120	+10	—	< 210	< 230	—	—	340	360	+20	—
6	F	54	0	500	50	60	+10	—	290	310	20	—	350	380	+30	—
7	M	50	0	600	110	120	+10	120	< 220	< 230	—	< 220	410	430	+20	430
8	M	56	0	600	70	80	+10	—	230	340	110	—	470	590	+120	—
9	F	47	0	600	90	110	+20	120	< 190	240	—	< 210	330	460	+130	480
10	M	32	0	600	50	70	+20	70	210	230	20	240	310	320	+10	330

Abbreviations: Acc P, accessory pathway; BCL, basic cycle length; AH, atrium-His interval; ERP_{AVN}, effective refractory period atrioventricular node; FRP_{AVN}, functional refractory period atrioventricular node; V, verapamil.

Table 2 *Effects of verapamil on initiation and termination of tachycardia*

Case No.	*BCL*	*Re-entry zone (atrium) (ms)*				*Tachy zone (atrium) (ms)*				*Termination of tachycardia with V*	*Increase in RR interval during tachycardia after V*
		Before V	*After V*	*Change*	*Oral V*	*Before V*	*After V*	*Change*	*Oral V*		
1	600	290–220	290–260	-40	—	290–220	290–260	-40	—	+	320→360
2	600	280–230	260–200	+10	300–200	280–230	260–200	+10	300–200	+	250→320
3	500	290–200	300–240	-30	—	290–200	300–240	-30	—	0	360→400
4	600	340–260	540–430	+30	360–280	340–260	540–430	+30	360–280	+	420→480
5	500	250–210	—	—	—	250–210	—	—	—	+	240→280
6	500	320–290	—	—	—	320–290	—	—	—	+	260→280
7	600	280–220	280–230	-10	290–240	280–220	280–320	-10	—	+	300→370
8	600	270–230	360–340	-20	—	270–230	360–340	-20	—	+	330→420
9	600	260–190	—	—	270–210	260–190	—	—	—	+	360→450
10	600	260–210	240–230	-40	240–220	260–210	240–230	-40	—	+	340→380

refractory period of the different parts of the pathway. Serum levels of verapamil were not determined during the acute or chronic studies.

Results

AV CONDUCTION

The AH interval, and the effective refractory period (ERP) and functional refractory period (FRP) of the AV node lengthened after verapamil (Table 1). The AH interval increased by 20±16 ms ($P<0{\cdot}001$); the FRP_{AVN} by 45±45 ms ($P<0{\cdot}001$).

VA CONDUCTION

All patients showed ventriculoatrial conduction during ventricular pacing. On applying the single test stimulation procedure, 3 patients (cases 1 to 3) showed no change in VA conduction time on shortening the V_1-V_2 interval up to the refractory period of the ventricle; in 2 (cases 2 and 3) the His bundle electrogram was seen to approach the atrial electrogram. In these 3 patients, who all had VA conduction over an accessory pathway, no change in effective refractory period of the VA conduction system was seen after verapamil administration. However, the ability to initiate tachycardia by a single ventricular premature beat at longer premature beat intervals (see below) suggests that verapamil resulted in lengthening of the ERP_{AVN} in the VA direction. In 4 patients (cases 5, 6, 7, and 8), the increase in VA conduction time on shortening the V_1-V_2 interval was found to be located in the V_2-H_2 interval, the H_2-A_2 interval remaining constant. None of these patients showed any change in these values after verapamil administration. In the remaining 3 patients (cases 4, 9, and 10) VA conduction time following premature stimuli increased on shortening the V_1-V_2 interval; in the absence of a His bundle electrogram the site of increase in V_2-A_2 interval could not be determined. In 2 of these patients (cases 4 and 5), apart from lengthening of the VA conduction time, the VA effective refractory period increased after verapamil by, respectively, 30 and 50 ms; case 4 was restudied after oral verapamil administration and showed a 40 ms increase in effective refractory period of the VA conduction system.

MECHANISM OF TACHYCARDIA

Atrial stimulation

As shown in Table 2, tachycardia could be initiated by a single atrial premature beat in all patients before verapamil. In cases 1 to 3, a gradual increase in A_2-H_2 interval was seen with increasing prematurity of the atrial test stimulus, with initiation of tachycardia at a critical A_2-H_2 interval. In the other 7 patients (cases 4 to 10) a sudden prolongation of the A_2-H_2 interval of 50 ms or more was seen when the A_2-H_2 interval of the latest premature beat able to initiate tachycardia was compared with the A_2-H_2 interval of the premature beat given 10 ms later. The width of the zone, during which an atrial test stimulus resulted in tachycardia, ranged from 30 to 90 ms. In cases 4 to 10, atrial activation in the His bundle lead during the first beat of tachycardia preceded or occurred simultaneously with ventricular activation. In cases 1 to 3, atrial activation occurred after ventricular activation.

In all patients verapamil was injected during tachycardia. They all showed (Table 2) an increase in RR interval with a maximum of 53±20 ms ($P<0{\cdot}001$). This increase in RR interval during tachycardia was found to be located in the AH interval only. No effect was noted on the HA interval during tachycardia. In 9 patients verapamil resulted in termination of tachycardia 9 seconds to 2½ minutes after the end of the injection. Tachycardia always ended with a P wave, suggesting that block occurred in the anterograde limb of the re-entry circuit. In one patient only alternation in AH interval (by 20 ms) was observed before termination of tachycardia (Vohra *et al.*, 1974a). None of our patients showed the emergence of premature beats before reversion of tachycardia (Vohra *et al.*, 1974b).

After intravenous verapamil no tachycardia could be initiated during atrial pacing in 3 patients (Table 2). An example is given in Fig 1, 2, and 3. The width of the tachycardia zone increased in 2 of the remaining 7 patients and decreased in 5. In all except case 2, the earliest atrial premature beat able to initiate tachycardia was later after verapamil because of the increase in length of the ERP_{AVN}.

Ventricular stimulation

Only in patients with an accessory pathway (cases 1 to 3) was it possible to initiate tachycardia by a single ventricular premature beat during ventricular pacing; the width of the tachycardia zone in these 3 patients measured, respectively, 80, 50, and 90 ms. In all 3, tachycardia could still be initiated after verapamil. In cases 2 and 3 the width of the tachycardia zone increased after verapamil administration by, respectively, 20 and 70 ms, suggesting lengthening of the effective refractory period of the AV node in the VA direction; no change was observed in case 1.

All patients (including cases 1 to 3) in whom tachycardia could still be initiated during atrial or ventricular pacing after verapamil showed a slower heart rate during tachycardia. This reduction in heart rate made it possible to terminate tachycardia by a single atrial premature beat in those patients where before verapamil two atrial premature beats were required to end tachycardia (Fig. 4).

Chronic oral verapamil administration

As shown in Tables 1 and 2, in the 5 patients studied, the effect of chronic oral verapamil administration was usually less than that of intravenous administration. However, in 2 patients (cases 7 and 10) tachycardia could not be initiated during oral administration of verapamil while this was still possible after intravenous administration of the drug.

In one patient (case 4) the pattern of sudden increase in A_2-H_2 interval on entering the tachycardia zone present before and after intravenous verapamil (Fig. 5) was no longer present during administration of verapamil (Fig. 6).

Discussion

Verapamil is an antiarrhythmic drug which received considerable attention because of its ability selectively to block the slow inward current in the isolated preparation (Kohlhardt *et al.*, 1972; Cranefield *et al.*, 1974; Wit and Cranefield, 1974; Zipes, 1975). Since both sinus and AV node

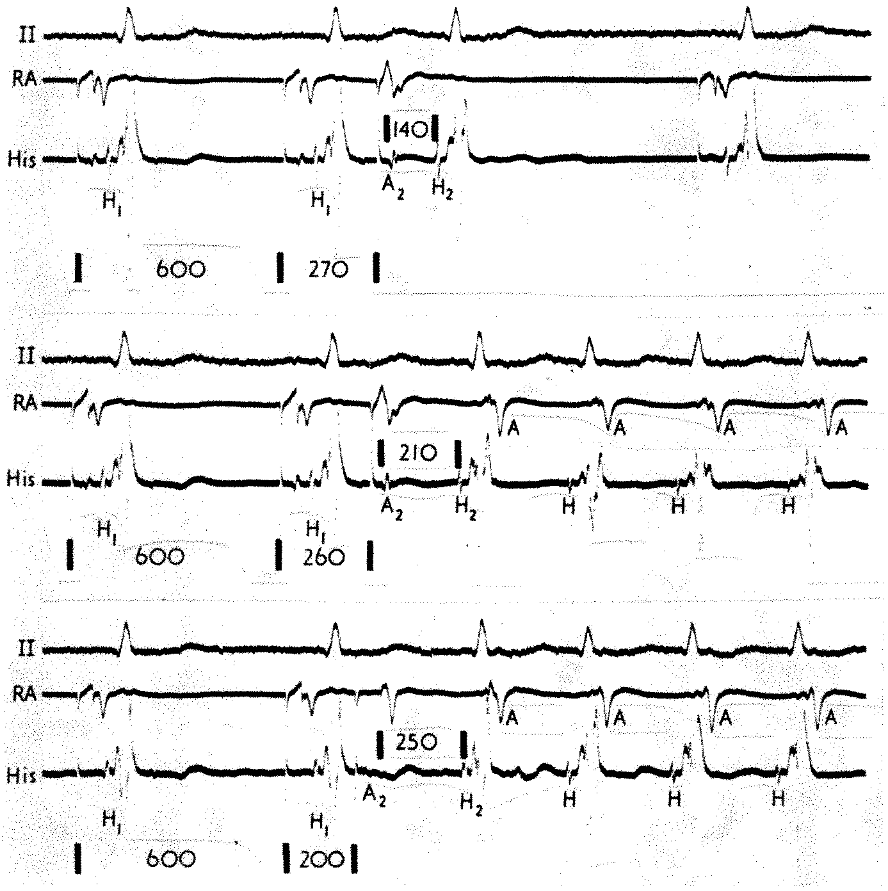

Fig. 1 *Case 9. Before verapamil. Initiation of tachycardia by a single atrial premature beat during atrial pacing at a basic cycle length of 600 ms. Three different premature beat intervals are shown. When the interval of the test pulse is changed from 270 to 260 ms, there is an increase in* A_2–H_2 *interval from 140 ms to 210 ms. This increase in* A_2–H_2 *interval is followed by tachycardia. Further increase in prematurity of the test pulse resulted in a gradual increase in* A_2–H_2 *interval followed by tachycardia.*

function are thought to be maintained by the operation of a slow channel mechanism, verapamil has been used for the treatment of supraventricular tachycardias. Our observations confirm previous observations on the effectiveness of intravenous verapamil in terminating reciprocal supraventricular tachycardia in man (Schamroth *et al.*, 1972; Krikler and Spurrell, 1974; Härtel and Hartikainen, 1976). In fact, the almost instantaneous effect of intravenous administration has made the drug our first choice of treatment if vagal manoeuvres fail to terminate paroxysmal supraventricular tachycardia.

As has previously been shown by Neuss and Schlepper (1971), Husaini *et al.* (1973), and Roy *et al.* (1974), verapamil lengthens the refractory period of the AV node and the transnodal conduction time. We found that both in patients with re-entrant AV nodal tachycardia and in patients with a concealed AV pathway, termination of

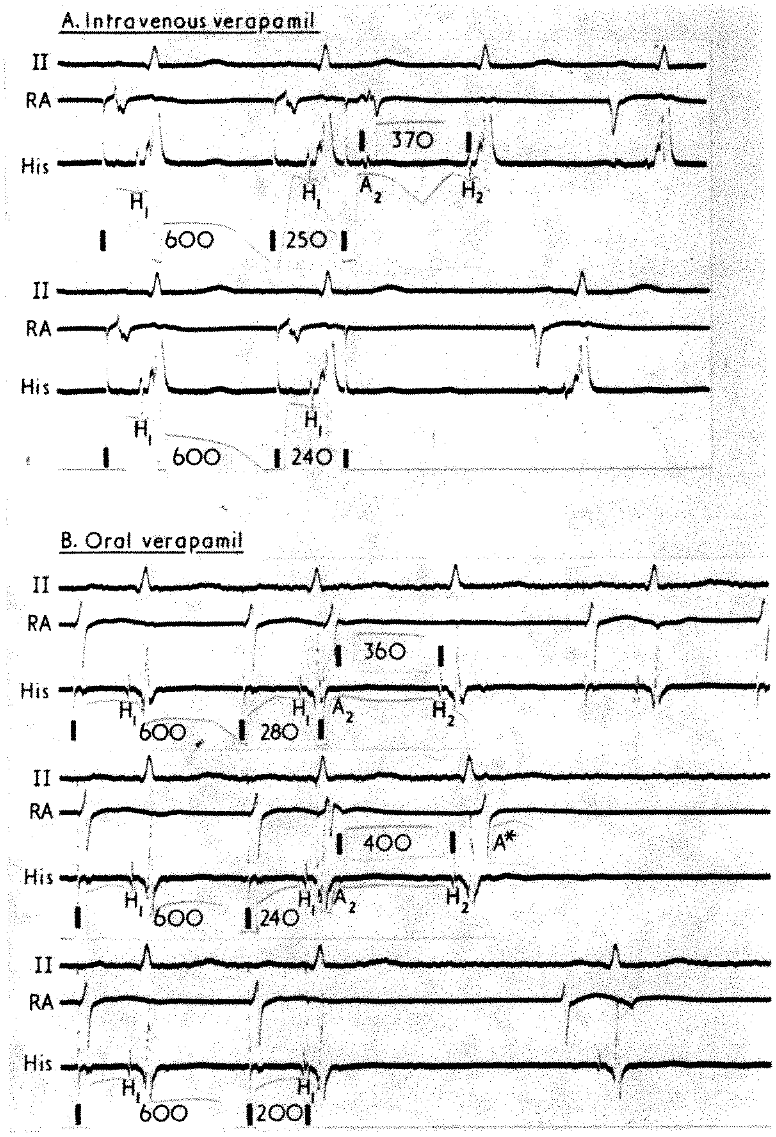

Fig. 2 *Case 9. (A) After intravenous verapamil, premature test stimuli given up to the effective refractory period of the right atrium (240 ms) are conducted to the bundle of His with greater delay than before verapamil and are not followed by tachycardia.*
(B) During oral verapamil administration, a premature stimulus at 280 ms is conducted with an A_2–H_2 *interval of 360 ms (150 ms longer than the* A_2–H_2 *interval at the time of initiation of tachycardia before verapamil, as in Fig. 1). A premature stimulus at 240 ms is conducted with an* A_2–H_2 *interval of 400 ms and is followed by a single atrial echo (A*). All atrial premature beats in the premature beat interval (*A_1–A_2*) range 270 to 200 ms (the ERP of the right atrium) were followed by a single atrial echo.*

tachycardia resulted from block in the anterograde AV nodal limb of the tachycardia circuit. Verapamil did not affect the retrograde pathway in any patient. This effect has previously been reported by Spurrell *et al.* (1974a) in patients with the WPW syndrome prone to circus movement tachycardia. In the view of the same authors (1974b), the absence of effect of verapamil on the VA limb of the tachycardia circuit implied that VA conduction was by concealed AV nodal bypass. However, we found that verapamil had no effect on the VA limb of the tachycardia circuit in patients fulfilling all the criteria of intranodal re-entry (Wellens and Durrer, 1975), including simultaneous activation during tachycardia of atrium and ventricle. In addition, during single test stimulation, an increase in HA interval was seen in only 2 patients. These observations suggest that the absence of effect of verapamil

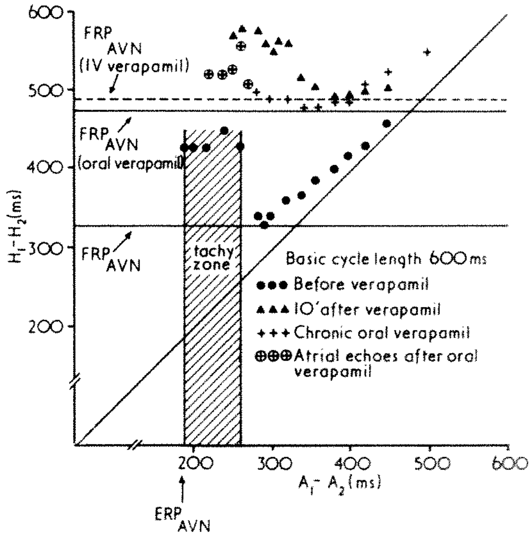

Fig. 3 *Case 9. Relation between A_1–A_2 interval and H_1–H_2 interval before and after intravenous verapamil, and during oral verapamil administration. Before verapamil premature beats given in the interval range 260 to 190 ms resulted in tachycardia. The FRP_{AVN} before verapamil measured 330 ms. After intravenous verapamil, tachycardias could not be initiated; the FRP_{AVN} increased to 490 ms. After oral verapamil tachycardias could not be initiated. Only single atrial echoes followed premature beats given in the interval range 270 to 200 ms. The FRP_{AVN} measured 470 ms.* →

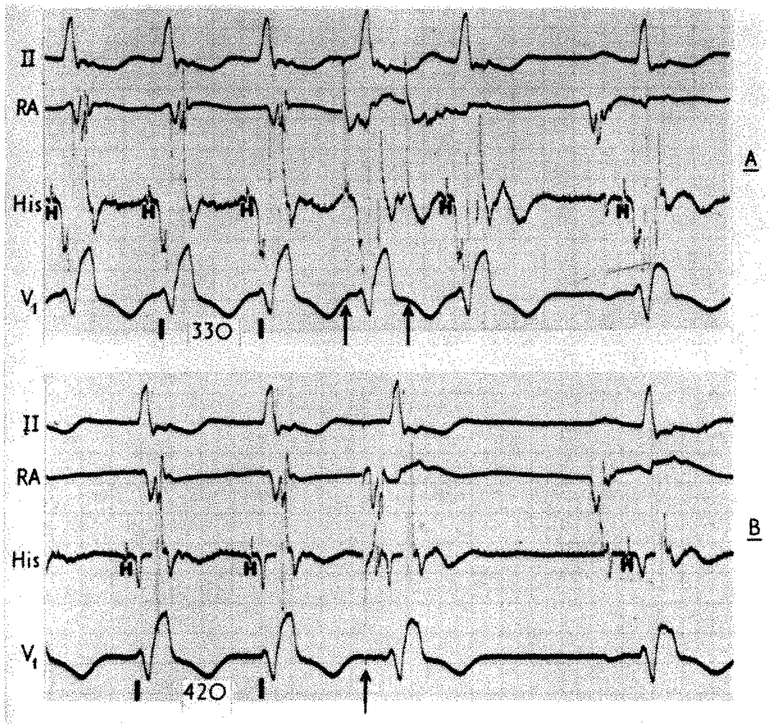

Fig. 4 *Case 8. AV nodal tachycardia (A) before and (B) after intravenous verapamil. Note: (1) increase in length of the tachycardia cycle from 330 ms to 420 ms; (2) localisation of the increase in cycle length in the AH interval; and (3) termination of tachycardia by a single atrial premature beat (single arrow) instead of two (2 arrows) because of slowing in rate of tachycardia after verapamil.*

on VA conduction does not prove VA conduction over an AV nodal bypass.

Our data do not confirm the explanation given by Wit and Cranefield (1974) for the effect of verapamil in preventing AV nodal tachycardia. In the rabbit heart they noted that verapamil resulted in such lengthening of the effective refractory period of the node that premature impulses could not enter the node early enough to be slowed sufficiently to initiate re-entry. As seen after digitalis administration (Wellens *et al.*, 1975; Wu *et al.*, 1975), our patients showed slowing in AV nodal transmission with verapamil despite lengthening of the effective refractory period of the node. They all showed maximal AH intervals which were of the same order as or even longer (Fig. 1 and 2) than those before verapamil. As shown in Fig. 2, it was still often possible to elicit single atrial echo beats after verapamil, as after digitalis. Apparently prolongation of the refractory period of the anterograde AV nodal part of the re-entry circuit prevented the atrial echo from returning to the ventricle and initiating tachycardia. When verapamil was injected during tachycardia, and also if tachycardia could still be initiated after the drug had been given, slowing of transmission through the anterograde AV nodal part of the tachycardia circuit resulted in slowing of the tachycardia. As has been pointed out by Denes *et al.* (1973) and Wu *et al.* (1974), this phenomenon of selective slowing of conduction through the AV node makes verapamil, like digitalis and propranolol, a drug that may actually favour initiation and perpetuation of tachycardia if VA conduction occurs over an accessory pathway. By delaying AV nodal conduction these drugs will increase the chance for the impulse to find the ventricular end of the accessory pathway excitable, thereby promoting VA conduction over this pathway and initiation of tachycardia.

In 2 of our patients short AH intervals were present. As previously described by Both *et al.* (1975), the effect of verapamil on the effective and functional refractory period of the AV node and AV nodal transmission time was less in these patients than in those with normal AH intervals. Though small, the increase in these measurements after verapamil suggests an anatomically small AV node or an intranodal short circuit rather than an AV nodal bypass fibre as the explanation for the short AH time in our 2 patients. Of practical im-

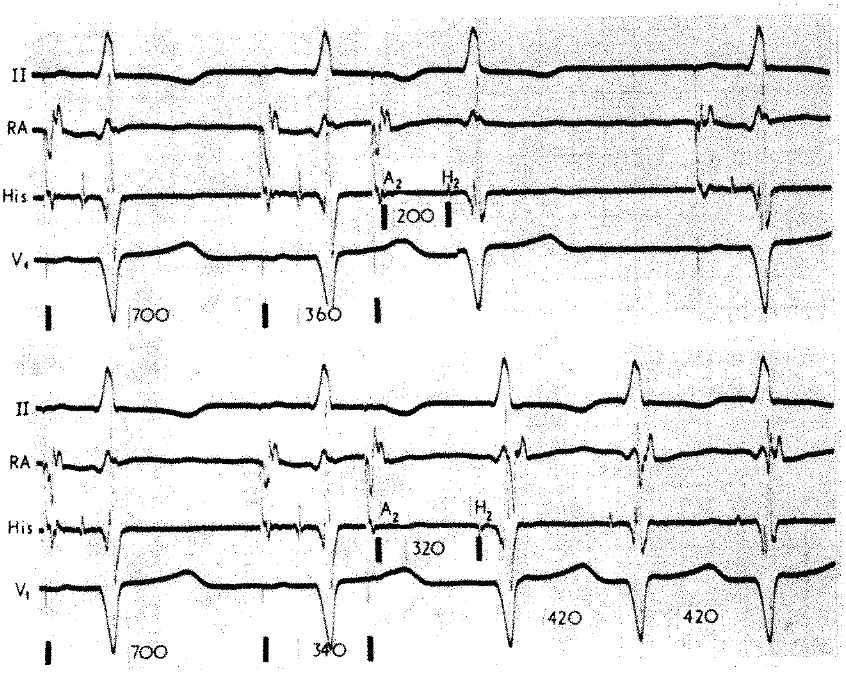

Fig. 5 *Case 4. Before verapamil. On changing the premature beat interval from 360 to 340 ms the A_2–H_2 interval increases from 200 to 320 ms, followed by tachycardia. This sudden increase in A_2–H_2 interval suggests the presence of double AV nodal pathways.*

portance was the observation that in both these patients the tachycardia could readily be terminated by verapamil. We have previously reported (Wellens *et al.,* 1975), a change in AV nodal transmission pattern after digitalis from a 'double pathway' curve into a 'smooth' curve (Denes *et al.,* 1973). In one patient (Fig. 5 and 6) in whom a 'double pathway' curve was still present after intravenous verapamil a smooth curve was obtained after chronic oral administration. Possible explanations for this phenomenon have been given elsewhere (Wellens *et al.,* 1975). In the 5 patients restudied after oral administration of verapamil, the same direction of changes (though less in degree) was found when the effects of intravenous and oral administration of the drug were compared. As with digitalis and AV nodal tachycardia (Wellens *et al.,* 1975), this suggests that data obtained after intravenous administration of verapamil can be used for selecting patients likely to benefit from chronic oral verapamil administration.

References

Amat, F., Denes, P., Wu, D., Pietras, R. J., and Rosen, K. (1974). The effects of atrial pacing site on A-V nodal function (abstract). *American Journal of Cardiology,* **33,** 123.

Batsford, W., Akhtar, M., Caracta, A. R., Josephson, M. E., Seides, S. F., and Damato, A. N. (1974). Effect of atrial stimulation site on the electrophysiological properties of the atrioventricular node in man. *Circulation,* **50,** 283–292.

Bender, F. (1967). Isoptin zur Behandlung der tachykarden Form des Vorhofflatterns. *Medizinische Klinik,* **62,** 634–636.

Bender, F., Kojima, N., Reploh, H. D., and Oelmann, G. (1966). Behandlung tachykarder Rhythmusstörungen des Herzens durch Beta-Rezeptorenblockade des Atrioventrikulargewebes. *Medizinische Welt,* **1,** 1120–1123.

Both, A., Seipel, L., and Loogen, F. (1975). Diagnostische Probleme beim L.G.L. Syndrom. In *His-Bündel-Elektrographie,* p. 147. Ed. by L. Seipel, F. Loogen, and A. Both. Schattauer Verlag, Stuttgart.

Cranefield, P. F., Aronson, R. S., and Wit, A. L. (1974). Effect of verapamil on the normal action potential and on a calcium-dependent slow response of canine cardiac Purkinje fibers. *Circulation Research,* **34,** 204–213.

Denes, P., Wu, D., Dhingra, R. C., Chuquimia, R., and Rosen, K. (1973). Demonstration of dual A-V nodal path-

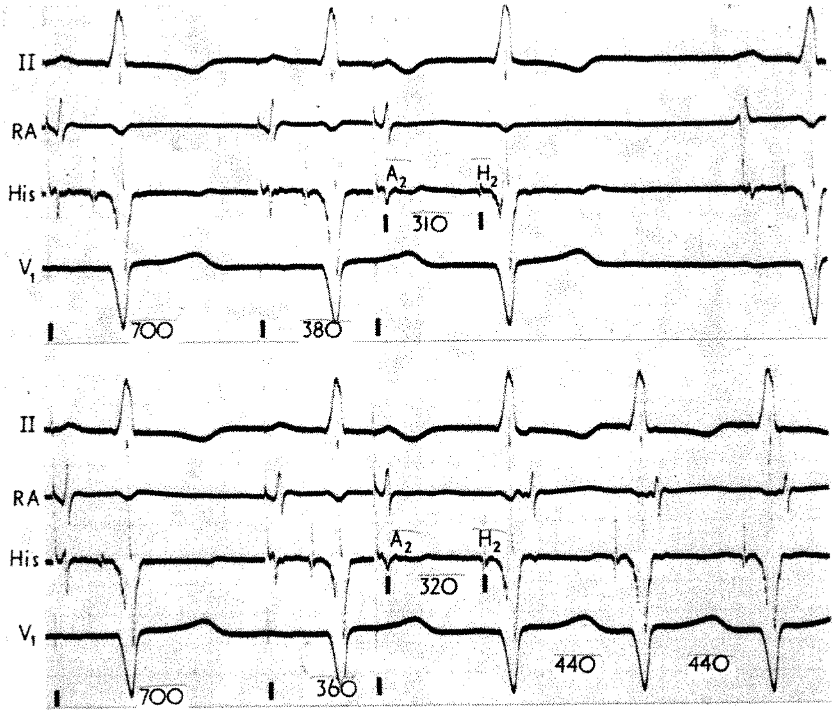

Fig. 6 *Case 4. During oral verapamil administration. On changing the premature beat interval from 380 to 360 ms the A_2–H_2 interval now increases by only 10 ms (from 310 to 320 ms). The latter premature beat is followed by tachycardia. Possible explanations for this phenomenon (change from a 'double pathway' curve into a 'smooth' curve) are given elsewhere (Wellens* et al., *1975).*

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ways in patients with paroxysmal supraventricular tachycardia. *Circulation,* **48,** 549–555.

Härtel, G., and Hartikainen, M. (1976). Comparison of verapamil and practolol in paroxysmal supraventricular tachycardia. *European Journal of Cardiology,* **4,** 87–90.

Husaini, M. H., Kvasnicka, J., Ryden, L., and Holmberg, S. (1973). Action of verapamil on sinus node, atrioventricular, and intraventricular conduction. *British Heart Journal,* **35,** 734–737.

Kohlhardt, M., Bauer, B., and Krause, H. (1972). Differentiation of the transmembrane Na and Ca channels in mammalian cardiac fibres by the use of specific inhibitors. *Pflügers Archiv für die gesamte Physiologie,* **335,** 309–322.

Krikler, D., and Spurrell, R. (1974). Verapamil in the treatment of paroxysmal supraventricular tachycardia. *Postgraduate Medical Journal,* **50,** 447–453.

Neuss, H., and Schlepper, M. (1971). Der Einfluss von Verapamil auf die atrio-ventrikuläre Uberleitung. Lokalisation des Wirkungsortes mit His-Bündel Elektrogrammen. *Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung,* **37,** 433–438.

Roy, P. R., Spurrell, R. A. J., and Sowton, E. (1974). The effect of verapamil on the cardiac conduction system in man. *Postgraduate Medical Journal,* **50,** 270–275.

Schamroth, L. (1971). Immediate effects of intravenous verapamil on atrial fibrillation. *Cardiovascular Research,* **5,** 419–424.

Schamroth, L., Krikler, D. M., and Garrett, C. (1972). Immediate effects of intravenous verapamil in cardiac arrhythmias. *British Medical Journal,* **1,** 660–662.

Spurrell, R. A. J., Krikler, D. M., and Sowton, E. (1974a). Effects of verapamil on electrophysiological properties of anomalous atrioventricular connexion in Wolff-Parkinson-White syndrome. *British Heart Journal,* **36,** 256–264.

Spurrell, R. A. J., Krikler, D. M., and Sowton, E. (1974b). Concealed bypasses of the atrioventricular node in patients with paroxysmal supraventricular tachycardia revealed by intracardiac electrical stimulation and verapamil. *American Journal of Cardiology,* **33,** 590–595.

Vohra, J., Hunt, D., Stuckey, J., and Sloman, G. (1974a). Cycle length alternation in supraventricular tachycardia after administration of verapamil. *British Heart Journal,* **36,** 570–576.

Vohra, J., Peter, T., Hunt, D., and Sloman, G. (1974b). Verapamil induced premature beats before reversion of supraventricular tachycardia. *British Heart Journal,* **36,** 1186–1193.

Wellens, H. J. J., and Durrer, D. (1975). The role of an accessory atrioventricular pathway in reciprocoal tachycardia. Observations in patients with and without the Wolff-Parkinson-White syndrome. *Circulation,* **52,** 58–72.

Wellens, H. J. J., Düren, D. R., Liem, K. L., and Lie, K. I. (1975). Effect of digitalis in patients with paroxysmal atrioventricular nodal tachycardia. *Circulation,* **52,** 779–788.

Wit, A. L., and Cranefield, P. F. (1974). Effect of verapamil on the sinoatrial and atrioventricular nodes of the rabbit and the mechanism by which it arrests re-entrant atrioventricular nodal tachycardia. *Circulation Research,* **35,** 413–425.

Wu, D., Denes, P., Dhingra, R., Khan, A., and Rosen, K. (1974). The effects of propranolol on induction of A-V nodal re-entrant paroxysmal tachycardia. *Circulation,* **50,** 665–677.

Wu, D., Wyndham, C., Amat-Y-Leon, F., Denes, P., Dhingra, R. C., and Rosen, K. (1975). The effects of ouabain on induction of atrioventricular nodal re-entrant paroxysmal supraventricular tachycardia. *Circulation,* **52,** 201–207.

Zipes, D. P. (1975). Recent observations supporting the role of slow current in cardiac electrophysiology. In *The Conduction System of the Heart,* p. 85. Ed. by H. J. J. Wellens, K. I. Lie, and M. J. Janse. Lea and Febiger, Philadelphia.

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British Heart Journal, 1977, **39**, 1067–1070

Vasodilator therapy in acute myocardial infarction

Use of sublingual isosorbide dinitrate

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The haemodynamic effect of a long-acting vasodilator isosorbide dinitrate has been studied in 10 patients after an acute myocardial infarct, all of whom had evidence of left ventricular failure. Left ventricular filling pressure measured as the mean pulmonary artery wedge pressure was raised in all patients and fell significantly from 20±6 to 13±5 mmHg ($P<0.001$) within 10 minutes of sublingual isosorbide dinitrate. This 35 per cent fall in left ventricular preload was accompanied by significant fall in mean pulmonary artery pressure from 30±7 to 20±4 mmHg ($P<0.001$) and mean right atrial pressure from 11±3 to 6±2 mmHg but cardiac output measured by thermodilution was unchanged. Mean systemic blood pressure was also significantly reduced. This improvement in left ventricular performance resulting from a reduction in left ventricular filling pressure and systemic blood pressure indicates that there may be a place for long-acting vasodilators in the treatment of acute myocardial infarction.

The relief of angina pectoris by vasodilators may be partly the result of the reduction in left ventricular work consequent upon a fall in venous and systemic blood pressure. The effect of such a reduction in left ventricular preload and afterload (both of which are determinants of myocardial oxygen consumption) has been reported in patients with acute myocardial infarction, using vasodilators such as sodium nitroprusside (Franciosa *et al.*, 1972) and phentolamine (Kelly *et al.*, 1973) but, recently, interest has been renewed in the use of nitrates (Delgado *et al.*, 1975; Williams *et al.*, 1975). A limiting factor is the short duration of action of glyceryl trinitrate though a topical ointment (Reichek *et al.*, 1974) and intravenous infusions have been used to overcome this (Flaherty *et al.*, 1976). Isosorbide dinitrate is an alternative nitrate with similar but much longer action, and has been used in angina pectoris and chronic left ventricular failure (Kovick *et al.*, 1976; Mantle *et al.*, 1976). Its effect was, therefore, investigated in patients with acute myocardial infarction, in whom there was evidence of acute left ventricular failure.

Patients and methods

Ten patients (9 male and 1 female) with a mean age of 62 (±9) years who had been admitted to the coronary care unit with an acute myocardial infarct were studied. The diagnosis was based on a typical history, serial changes in a 12-lead electrocardiogram with new Q waves, and an appropriate rise and fall in cardiac enzymes (World Health Organization, 1959). All patients had a portable posteroanterior chest *x*-ray film shortly after admission.

Six patients had anterior myocardial infarcts, three inferior infarcts, and one left bundle-branch block. Two patients had also had a previous myocardial infarction. Clinical evidence of left ventricular failure was present in all patients. Seven had third or fourth heart sounds, 9 had radiological changes of pulmonary oedema, and most had audible basal crepitations.

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HAEMODYNAMIC MEASUREMENTS

After informed consent had been obtained, a 7F Swan Ganz flow directed thermodilution catheter was passed under fluoroscopic control from an anticubital vein into the pulmonary artery. The patency of the catheter was maintained by a slow infusion of heparin in 5 per cent dextrose (5000 units 12-hourly). The catheter was connected to an Elcomatic transducer and electromanometer from which measurements of mean right atrial, pulmonary artery, and pulmonary artery wedge pressure were made, the latter being obtained by intermittent inflation of the catheter balloon. All measurements were made with the patient supine and free from pain, using the midpoint of the anteroposterior diameter of the chest as the zero reference level. The initial study was made within 24 hours of infarction in 9 patients, 4 of whom had a second study on the following day. No diuretics or analgesics had been administered within 4 hours of the study.

Cardiac output was measured using the thermodilution technique (Ganz and Swan, 1972) and the St. Thomas's Cardiac Output Computer (Cardiovascular Instruments Ltd. 3750). On each occasion the cardiac output was measured in triplicate and the mean calculated. The patients were attached to a Sanborn bedside electrocardiographic monitor from which the heart rate was recorded. Systemic blood pressure was measured with a standard sphygmomanometer cuff using the first and fourth Korotkoff sounds for systolic and diastolic pressure, respectively.

The intracardiac pressures, cardiac output, heart rate, and systemic blood pressure were measured at the start and at the end of a 30-minute control period. If the baseline measurements were unchanged 5 mg isosorbide dinitrate was given sublingually and further measurements made after 5 to 10 minutes, 25 to 30 minutes, 1 hour and 2 hours.

The following calculations were made:

Cardiac index (CI) =

$$\frac{\text{Cardiac output (CO)}}{\text{body surface area (BSA)}}\ (\text{l/min per m}^2)$$

Systemic vascular resistance =

$$\frac{\text{mean BP–mean RAP}}{\text{CO}}\ (\text{units})$$

where RAP = right atrial pressure

Left ventricular stroke work index (LVSWI) = SI × (MSP–LVFP) × 0·0136 g m/beat per m² BSA where SI (stroke index) =

$$\frac{\text{CI}}{\text{heart rate}}$$

MSP (mean systolic blood pressure) = 0·8 (systolic BP–diastolic BP) × diastolic BP and LVFP (left ventricular filling pressure) = mean pulmonary artery wedge pressure (Walker *et al.*, 1973).

The method of statistical analysis used was the paired t test.

Results

A total of 14 studies was made in the 10 patients all of whom had a raised mean pulmonary artery wedge pressure (greater than 12 mmHg) during the control period. The striking haemodynamic effect was a 37 per cent reduction in mean pulmonary artery wedge pressure from 20 ± 6 to 13 ± 5 mmHg within 10 minutes of drug administration. This change which is highly significant ($P < 0{\cdot}001$) was accompanied by a highly significant reduction in mean pulmonary artery pressure from 29 ± 7 to 21 ± 6 mmHg ($P < 0{\cdot}001$) (Fig. 1). There was also a fall in the mean right atrial pressure from 11 ± 3 to 6 ± 2 mmHg. This effect persisted for between 1 and 2 hours and for some patients longer.

Fig. 2 shows a small rise in heart rate of 5 beats per minute at 10 minutes and a significant fall in mean blood pressure. The change in systolic blood pressure was greater than in diastolic pressure and indeed diastolic blood pressure was not significantly altered.

Cardiac output in individual patients varied after isosorbide dinitrate but the maximal reduction in mean cardiac output for the group of 3·4 to 3·3 l/min was not significant (Fig. 2). Systemic vascular resistance and left ventricular stroke work index both fell slightly but did not reach levels of statistical significance (Fig. 3) but a significant fall in pulmonary vascular resistance occurred at 30 minutes.

There were no complications of treatment. Two patients had a diuresis during the 4 hours after isosorbide; both these patients were breathless and were symptomatically improved.

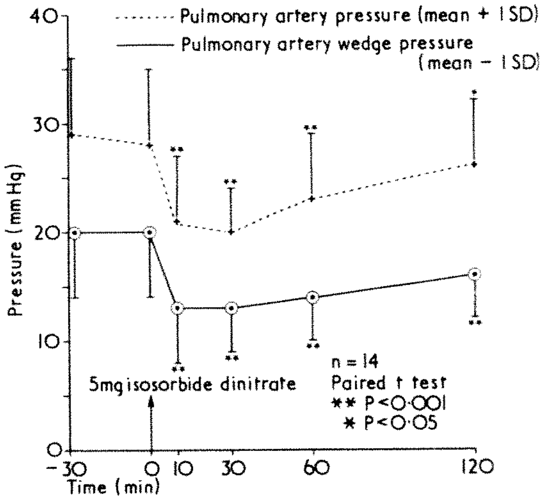

Fig. 1 *This shows the mean (± SD) change in mean pulmonary artery and pulmonary artery wedge pressures after 5 mg isosorbide dinitrate.*

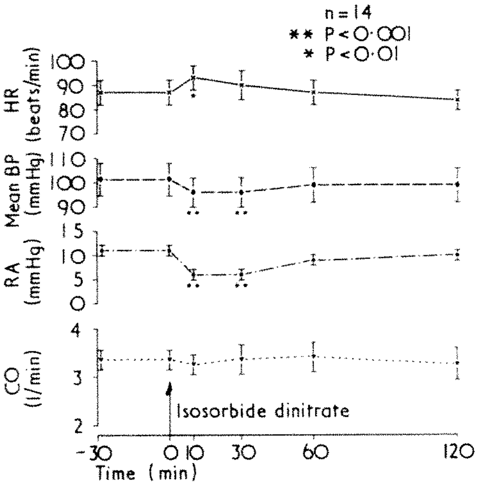

Fig. 2 *This shows the mean (± SEM) change in heart rate, mean blood pressure, mean right atrial pressure, and cardiac output after 5 mg isosorbide dinitrate.*

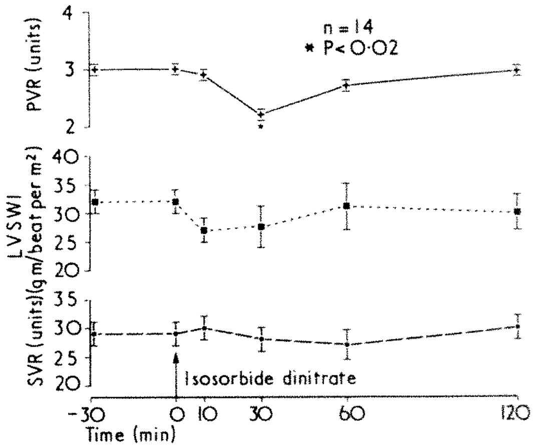

Fig. 3 *This shows the mean (± SEM) change in pulmonary vascular resistance (PVR), left ventricular stroke work index (LVSWI), and systemic vascular resistance (SVR).*

Discussion

The management of left ventricular failure after acute myocardial infarction remains a therapeutic problem. Patients with raised left ventricular end-diastolic pressure and low cardiac index have a higher mortality than other patients in spite of conventional therapy with inotropic agents (Scheidt *et al.*, 1973). In addition not all patients respond to diuretics, and studies with frusemide (Kiely *et al.*, 1973) suggest that as many as 50 per cent fail to obtain reduction in left ventricular filling pressure.

In the present study we have shown the beneficial haemodynamic effect of alternative treatment using a long acting nitrate as a vasodilator. Sublingually, isosorbide dinitrate produces a rapid fall in left ventricular preload and systemic blood pressure in all patients within 10 minutes, with a significant effect persisting for 2 hours. This occurred with only a slight initial increase in heart rate and no significant alteration in cardiac output. The likely benefits to the myocardium of the considerable fall in left ventricular filling pressure are a reduction in left ventricular end-diastolic volume (Willis *et al.*, 1976) and left ventricular wall tension with a subsequent fall in myocardial oxygen demand. This effect on oxygen requirement is in direct contrast to that produced by positive inotropic agents. Nitrates are in addition coronary vasodilators and, either by this mechanism or as a result of the fall in preload, increase blood flow to the ischaemic areas of myocardium (Becker *et al.*, 1971). The net effect after acute myocardial infarction may be a limitation in infarct size, and recent ST segment mapping studies by Flaherty *et al.* (1976) lend support to this theory.

Response to vasodilators may depend on the initial haemodynamic measurements. Their effect in reducing left ventricular preload is similar in all patients, but those with the highest initial left ventricular filling pressure appear to obtain the greatest reduction. The effect on left ventricular stroke work is more variable. Chatterjee *et al.* (1972) and Gold *et al.* (1972) report a decrease in left ventricular stroke work when this is normal before treatment, but an increase in left ventricular stroke work in patients with severe pump failure, in whom this is low before treatment. Similar findings have been reported in chronic cardiac failure (Mikulic *et al.*, 1975; Mantle *et al.*, 1976).

Little is known of the renal effects of isosorbide and other vasodilators, but a diuresis was observed in 2 patients in our series and by other authors (Mantle *et al.*, 1976). Isosorbide has been regarded as a mild osmotic diuretic (Lant, 1975) but this requires further study.

The exact place of vasodilators has still to be defined in acute myocardial infarction, but isosorbide dinitrate appears to be an alternative therapeutic agent in those patients with left ventricular failure who do not respond to diuretics. Some improvement in short-term prognosis has been achieved with chronic vasodilator treatment in patients with 'pump' failure (Chatterjee *et al.*, 1976), but its use in less severe cases of myocardial infarction will depend on further evaluation of its effect in limiting infarct size.

References

Becker, L. C., Fortuin, W. J., and Pitt, B. (1971). Effects of ischemia and anti-anginal drugs on the distribution of radio active microspheres in the canine left ventricle. *Circulation Research,* **28,** 263–269.

Chatterjee, K., Parmley, W. W., Ganz, W., Forrester, J., Walinsky, P., Crexells, C., and Swan, H. J. C. (1973). Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. *Circulation,* **48,** 1183–1193.

Chatterjee, K., Swan, H. J. C., Kaushik, V. S., Jobin, G., Magnusson, P., and Forrester, J. S. (1976). Effects of vasodilator therapy for severe pump failure in acute myocardial infarction on short term and late prognosis. *Circulation,* **53,** 797–802.

Delgado, C. E., Pitt, B., Taylor, D. R., Weisfeldt, M. L., and Kelly, D. T. (1975). Role of sublingual nitroglycerin in patients with acute myocardial infarction. *British Heart Journal,* **37,** 392–396.

Flaherty, J. T., Come, P. C., Baird, M. G., Rouleau, J., Taylor, D. R., Weisfeldt, M. L., Greene, H. L., Becker, L. C., and Pitt, B. (1976). Effects of intravenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction. *British Heart Journal,* **38,** 612–621.

Franciosa, J. A., Guiha, N. H., Limas, C. J., Rodriguera, E., and Cohn, J. (1972). Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet,* **1,** 650–654.

Ganz, W., and Swan, H. J. C. (1972). Measurement of blood flow by thermodilution. *American Journal of Cardiology,* **29,** 241–246.

Gold, H. K., Leinbach, R. C., and Sanders, C. A. (1972). Use of sublingual nitroglycerin in congestive failure following acute myocardial infarction. *Circulation,* **46,** 839–845.

Kelly, D. T., Delgado, C. E., Taylor, D. R., Pitt, B., and Ross, R. S. (1973). Use of phentolamine in acute myocardial infarction associated with hypertension and left ventricular failure. *Circulation,* **47,** 729–735.

Kiely, J., Kelly, D. T., Taylor, D. R., and Pitt, B. (1973). The role of furosemide in the treatment of left ventricular dysfunction associated with acute myocardial infarction. *Circulation,* **48,** 581–587.

Kovick, R. B., Tillisch, J. H., Berens, S. C., Bramowitz, A. D., and Shine, K. I. (1976). Vasodilator therapy for chronic left ventricular failure. *Circulation,* **53,** 322–328.

Lant, A. F. (1975). Which diuretic? *Prescribers' Journal,* **15,** 126–137.

Mantle, J. A., Russell, R. O., Moraski, R. E., and Rackley, C. E. (1976). Isosorbide dinitrate for the relief of severe heart failure after myocardial infarction. *American Journal of Cardiology,* **37,** 263–268.

Mikulic, E., Franciosa, J. A., and Cohn, J. N. (1975). Comparative hemodynamic effects of chewable isosorbide dinitrate and nitroglycerin in patients with congestive heart failure. *Circulation,* **52,** 477–482.

Reichek, N., Goldstein, R. E., Redwood, D. R., and Epstein, S. E. (1974). Sustained effects of nitroglycerin ointment in patients with angina pectoris. *Circulation,* **50,** 348–352.

Scheidt, S., Wilner, G., Fillmore, S., Shapiro, M., and Killip, T. (1973). Objective haemodynamic assessment after acute myocardial infarction. *British Heart Journal,* **35,** 908–916.

Walker, A. A., Janicki, J. S., Weber, K. T., Russell, R. O., and Rackley, C. E. (1973). Equations for the calculation of mean ejection pressure. *Cardiovascular Research,* **7,** 567–571.

Williams, D. O., Amsterdam, E. A., and Mason, D. T. (1975). Hemodynamic effects of nitroglycerin in acute myocardial infarction. *Circulation,* **51,** 421–427.

Willis, W. H., Russell, R. O., Mantle, J. A., Ratshin, R. A., and Rackley, C. E. (1976). Hemodynamic effects of isosorbide dinitrate vs nitroglycerin in patients with unstable angina. *Chest,* **69,** 15–22.

World Health Organization (1959). *World Health Organization. Technical Report Series,* No. 168.

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Two-dimensional echocardiography with a wide angle (60°) sector scanner[1]

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A wide angle (60°) sector scanner producing a real-time two-dimensional echocardiogram has been used to examine healthy infants, children, and adults. Its method of use is described and findings from longitudinal and transverse scans are presented.

The points of difference between the various types of electronic and mechanical two-dimensional scanning systems are discussed. This equipment minimises problems of chest contact and rib and lung interference and, by providing echocardiograms of high line density from a wide angle, is a suitable real-time two-dimensional scanning system for examining patients of all ages.

Echocardiography is an established technique in the assessment of congenital and acquired heart disease (Feigenbaum, 1972). Since Edler and Hertz (1954) first recorded the movements of the heart walls it has been found that it is possible using time-position echocardiography to recognise the walls of both ventricles, the left atrium, and the cusps of the atrioventricular and semilunar valves. In recent years real-time two-dimensional systems have been introduced for echocardiography. Multiple element systems have been developed (Bom *et al.*, 1973) using electronic switching between transducers in a linear array and (von Ramm and Thurstone, 1976) an electronic steered beam; versions of these and other multiple element systems are commercially available. Mechanical two-dimensional scanning systems in which a single transducer is rapidly oscillated through an arc of a circle have also been produced (Griffith and Henry, 1974; Nishimura *et al.*, 1976; Shaw *et al.*, 1976). The structures previously visualised by time-position echocardiography have been identified by two-dimensional systems and confirmed by contrast studies (Sahn *et al.*, 1974b). In addition these systems have allowed identification of the main pulmonary artery, but reports have differed on the appearance of the great arteries when seen in transverse section at their origins (Sahn *et al.*, 1974b; Henry *et al.*, 1975).

This report summarises our technique and experience in examining the normal heart using a mechanical real time wide-angle (60°) sector scanner.

Equipment

The ultrasonic equipment used is a hand-held mechanical 60° sector scanner in which an oscillating transducer is ultrasonically coupled to the patient through an oil-filled cell which also separates the patient from the movement of the transducer (Shaw *et al.*, 1976). Developments since the original description of this equipment permit the use of interchangeable transducers for work with adults, children, and neonates. The specifications of these transducers are 2·5 MHz 15 mm diameter, 2·5 MHz 12·5 mm diameter, and 5 MHz 6 mm diameter and they are focused for optimum performance in the ranges 8 to 12 cm, 5 to 10 cm and 2 to 4 cm, respectively. The scanner is used in conjunction with a Nuclear Enterprises Diasonograph (NE 4200) which has minor modifications to permit control of the transmitter pulse generator from the scanner interface unit and to allow the interface unit to gate the storage display under electrocardiographic control from the Diasonograph Cardiac Module. The display now consists of 128 equally spaced lines of information in each complete oscillation of the transducer; at maximum

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speed 25 frames of 64 lines are generated per second. The echocardiogram is normally viewed from the variable persistence monitor in its 'conventional' mode, through a television camera and monitor system, and recorded on a video recorder controlled with a foot-operated switch. Electrocardiographic information is included in the telerecording by means of a light which flashes in time with pulses from the electrocardiographic unit and by a digital indication of elapsed time after the electrocardiographic pulse. An alternative viewing system, which provides a static view of the heart and permits immediate photography, is provided by electrocardiographic controlled gating of the storage monitor. The display may be rewritten once in each heart cycle, at any point in the cycle, and when an appropriate view has been selected it can be stored for inspection or photography. All the illustrations in this report were obtained by this technique, but it is also possible to photograph still frame pictures from the television system. In normal use, with the patient supine, the weight of the scanner is supported by a spring tension cord device which hangs from a single track above him. This system permits free tilting and rotation of the scanner to any normally required position. This and the use of a foot-operated switch on the tape recorder allows the examination to be carried out by a single operator.

Method

The scanning planes employed are longitudinal and transverse. Because of the variability of the axis and position of the heart these planes cannot be based on standard thoracic cage sites, but rather on approximately standard views of the heart which the operator obtains by altering the position and angulation of the scanner in such a way as to make allowances for differences in cardiac position and chest configuration.

Longitudinal scans from normal subjects are illustrated in Fig. 1. The anterior mitral valve leaflet is used as a landmark to obtain this scan which corresponds to the standard time-position sweep from the mitral valve leaflets to the aorta. Such a section is most frequently obtained with the scanning head in the 4th left interspace at the left sternal edge, the scanning plane being perpendicular to the chest wall and directed towards the right shoulder. If satisfactory views are not obtained in this position the scanning head is moved to the 5th or 3rd interspace and, if necessary, further lateral from the left sternal edge. In each position the scanner is rotated and tilted to obtain an optimal view. The mitral valve cusps, and aorta and aortic valve cusps cannot always be seen in a single plane and minor alterations in transducer angulation may be required to display these structures individually. In adults the apical region of the left ventricle is visualised by tilting the scanner inferiorly or positioning it in a lower interspace. After a satisfactory longitudinal scan has been obtained, the scanner is held on the same site and rotated through approximately 90° to obtain a low transverse scan through the body of the left ventricle. In this position a sweep performed from the apex towards the base of the heart as with conventional single crystal echocardiography allows visualisation of the entire length of the posterior wall of the left ventricle. This position is the best for obtaining a section through the mitral valve orifice, the anterior and posterior cusps being readily visualised (Fig. 2). Tilting the plane of scan to the right brings the right ventricle and tricuspid valve into view anterior to the ventricular septum. The origins of the great arteries are most clearly identified in a high transverse scan, obtained with the transducer moved one interspace higher to position the aorta at the level of the valve, as identified by its cusps, in the centre of the scanning arc. The aorta cut in transverse section (Fig. 3) is seen as an approximately circular echo free space with the valve cusps as a central linear echo in diastole which disappears in systole. In the normal heart the right ventricular outflow crosses the aortic root obliquely before passing posteriorly and to the left as the main pulmonary artery. For assessment of the relations and sizes of the great arteries the plane of scan in the high transverse view is altered to lie along the right ventricular outflow and through the main pulmonary artery, by angling the scanner towards the lateral third of the left clavicle and tilting it superiorly. The high transverse scan thus obtained (Fig. 3) shows the right ventricular outflow as an echo free space passing anterior to and then to the left of the aorta as the main pulmonary artery with the echoes from the cusps of the pulmonary valve indicating the transition between them. The pulmonary valve as a rule lies anterior and to the left of the aorta though in infants it may lie directly anterior to the aortic valve. A scan through the right ventricular outflow and main pulmonary artery may section the aorta somewhat obliquely rather than transversely and minor alterations in the plane of scan are then required to show the aorta in direct transverse section. Since it is not always possible to obtain optimal views of both great arteries and semilunar valves in a single plane, the operator's impression of their relations as the scanning plane is altered may be necessary for correct interpretation of the examination. In our experience with normal subjects a high transverse

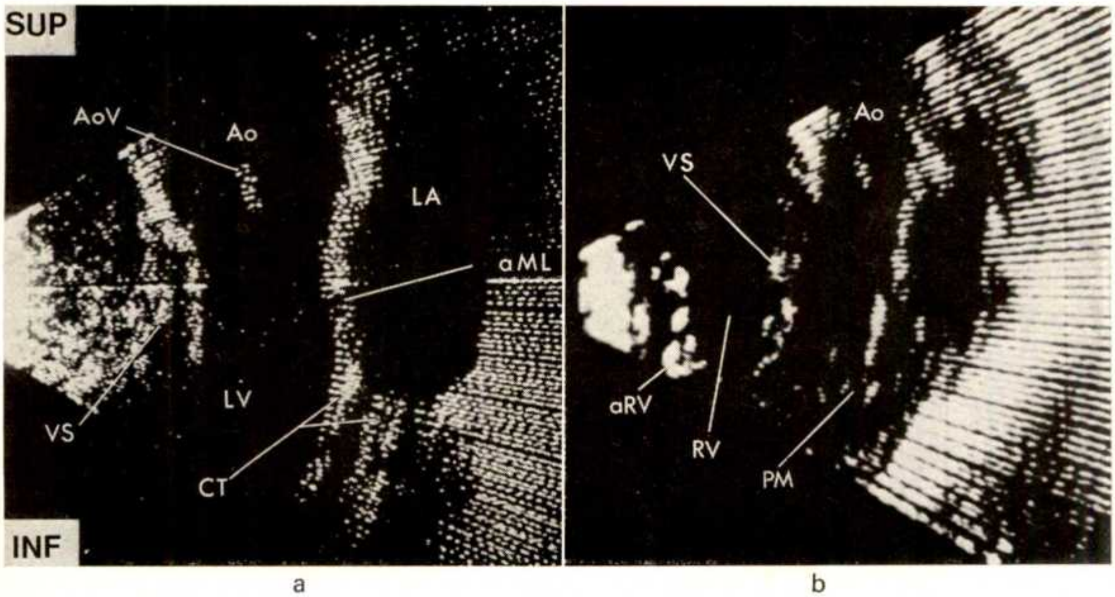

Fig. 1 *Longitudinal scans from normal subjects. (a) Adult in early diastole showing aortic valve closed and mitral valve about to open. (b) Infant weighing 2·9 kg, heart rate 150 per minute, in mid-diastole with mitral valve open. Ao, aortic root; AoV, aortic valve cusps; VS, ventricular septum; LA, left atrium; aML, anterior mitral leaflet; LV, left ventricle; CT, chordae tendineae; aRV, anterior right ventricular wall; PM, papillary muscle.*

scan does not show the two great arteries simultaneously as circular spaces with central cusp echoes.

Discussion

The recent introduction of two-dimensional scanning systems as an adjunct to conventional single crystal echocardiography has widened the scope, and thus the usefulness, of echocardiographic examination. Two basic systems were initially devised, the multiple element array (Bom *et al.*, 1973) and the mechanical sector scanner (Griffith and Henry, 1974; Nishimura *et al.*, 1976; Shaw *et al.*, 1976). Recently, an electronic steered beam system scanning a 60° sector has been developed (von Ramm and Thurstone, 1976). Sector scanners, because of their relatively small area of skin contact, minimise the interference presented by ribs and lungs. Problems of poor contact and patient discomfort caused by transducer movement, reported with some mechanical scanners (Griffith and Henry, 1974; Nishimura *et al.*, 1976), have been largely overcome by the oil-filled cell incorporated within our scanner (Shaw *et al.*, 1976), and in the electronically steered beam system. Mechanical sector

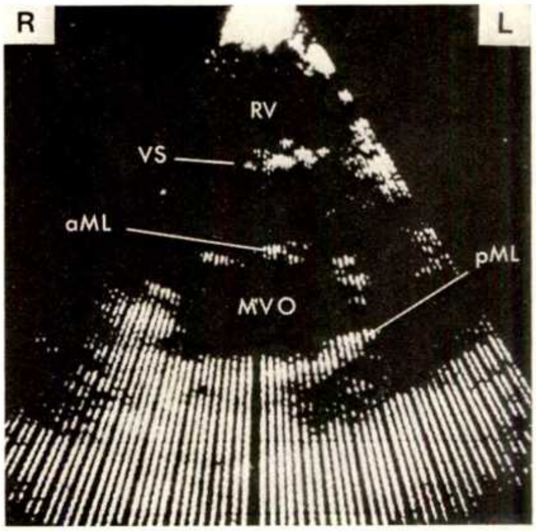

Fig. 2 *Transverse scan from normal adult subject at the level of the tips of the mitral valve. This view in early diastole shows the orifice of the partially open mitral valve. L and R: subject's left and right sides; RV, right ventricle; MVO, mitral valve orifice; aML, anterior mitral valve leaflet; pML, posterior mitral valve leaflet; VS, ventricular septum.*

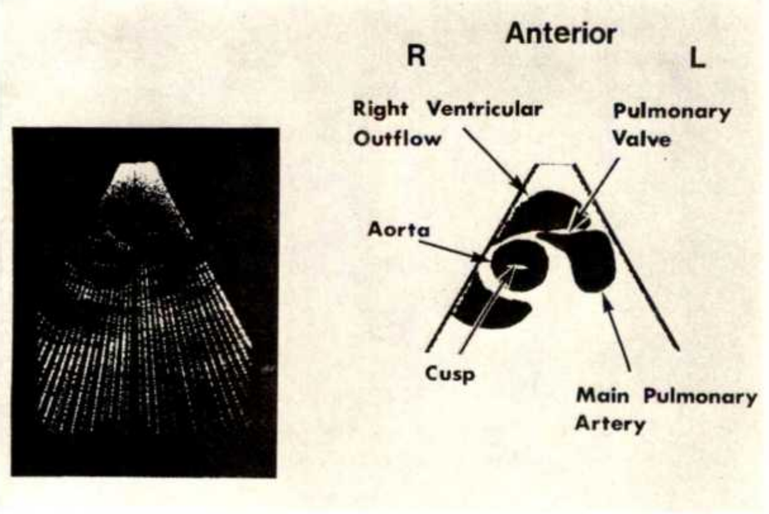

Fig. 3 *High transverse view through the right ventricular outflow and main pulmonary artery.*

scanners also have the advantage of using conventional circular transducers which, unlike the multiple element systems and the rectangular arrays of steered beam systems, give optimum resolution both within the plane of scan and at right angles to this plane. The high line density (128/60° with this system) in the near field of the mechanical scanner produces particularly clear pictures in infants, whereas the phased array system described by von Ramm and Thurstone (1976) is unable to record the proximal 30 to 40 mm of the scan. The clinical importance of these points is illustrated in Fig. 1b, which shows the aorta with a diameter of about 8 mm to be clearly resolved and not overlaid by echoes from adjacent structures; the right ventricular wall is clearly visualised only 14 mm from the scanner and all the structures of interest are within 40 mm. This capacity to produce well-resolved images of small objects close to the transducer is of particular importance in studying infants with congenital heart disease. The main disadvantage of sector scanners, a rather narrow near field of view, is partly balanced by the increased line density in the near field. There is also wider coverage of deeper structures; with the 60° scanning angle a posterior heart wall lying 80 mm deep in the chest is imaged over a length of 100 mm. Structures lying behind the sternum can be seen from a parasternal position. We have found that our system gives a satisfactory view of the posterior wall of the left ventricle in longitudinal and transverse sections, but the scanner may have to be tilted headwards if the aorta and the whole posterior wall of the left ventricle are to be seen in one plane. For a longitudinal view of the entire length of the ventricular septum the scanner may have to be moved between two sites. The aorta, right ventricular outflow, and main pulmonary artery are adequately shown in a single transverse scan within the 60° scanning angle.

The use of a multiple element system and of a 30° sector scanner in normal and abnormal hearts has been extensively reported (Sahn *et al.*, 1974a, b; Henry *et al.*, 1975). To a certain extent the findings appear to have been influenced by the technique used. Sahn *et al.* (1974a) with a multiple element system use standard positions on the chest to obtain their scans, but the present findings are more in accord with those of Henry *et al.* (1975) who adjust the plane of scan to obtain optimal views, and use different interspaces and scanning angles as required. The longitudinal scan, in accordance with previous reports, provides an image of all the structures shown in the conventional sweep of time-position echocardiography, but with the advantage that anatomical relations are more clearly defined. The low transverse sweep displays the posterior wall of the left ventricle and much of the anterior wall but distinct views of the lateral walls may not always be obtained; the mid-position of this sweep shows the entire mitral valve orifice. In the high transverse scan, adjusted to lie along the right ventricular outflow, the aorta is recorded in transverse section with the right ventricular outflow crossing anterior to it before turning posteriorly to its left as the main pulmonary artery. This appearance is similar to that reported by Henry *et al.* (1975). Our transverse scans do not show the great arteries simultaneously as circular spaces with central cusp echoes as implied by Sahn *et al.* (1974b); this difference could be explained by the better lateral resolution of single element scanners.

We conclude that sector scanners provide views of all the major structures of the heart and that our 60° mechanical system with its coupling cell and interchangeable transducers yields satisfactory two-dimensional displays of the heart at all ages and without discomfort to the patient.

References

Bom, N., Lancée, C. T., van Zwieten, G., Kloster, F. E., and Roelandt, J. (1973). Multiscan echocardiography. 1. Technical description. *Circulation,* **48,** 1066–1074.

Edler, I., and Hertz, C. H. (1954). The use of ultrasonic reflectoscope for the continuous recording of movements of heart walls. *Kungliga Fysiografiska Sällskapets i Lund Forhandlingar,* **5,** 24–27.

Feigenbaum, H. (1972). *Echocardiography.* Lea and Febiger, Philadelphia.

Griffith, J. M., and Henry, W. L. (1974). A sector scanner for real time two-dimensional echocardiography. *Circulation,* **49,** 1147–1152.

Henry, W. L., Maron, B. J., Griffith, J. M., Redwood, D. R., and Epstein, S. E. (1975). Differential diagnosis of anomalies of the great arteries by real-time two-dimensional echocardiography. *Circulation,* **51,** 283–291.

Nishimura, K., Hibi, N., Kato, T., Fukui, Y., Arakawa, T. Tatematsu, H., Miwa, A., Tada, H., Kambe, T., Nakagawa, K., and Takemura, Y. (1976). Real-time observation of cardiac movement and structures in congenital and acquired heart diseases employing high-speed ultrasonocardiotomography. *American Heart Journal,* **92,** 340–350.

Sahn, D. J., Terry, R., O'Rourke, R., Leopold, G., and Friedman, W. F. (1974a). Multiple crystal cross-sectional echocardiography in the diagnosis of cyanotic congenital heart disease. *Circulation,* **50,** 230–238.

Sahn, D. J., Williams, D. E., Shackelton, S., and Friedman, W. F. (1974b). The validity of structure identification for cross-sectional echocardiography. *Journal of Clinical Ultrasound,* **2,** 201–216.

Shaw, A., Paton, J. S., Gregory, N. L., and Wheatley, D. J. (1976). A real time 2-dimensional ultrasonic scanner for clinical use. *Ultrasonics,* **14,** 35–40.

Von Ramm, O. T., and Thurstone, F. L. (1976). Cardiac imaging using a phased array ultrasound system. 1. System design. *Circulation,* **53,** 258–267.

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Two-dimensional sector scanner echocardiography in cyanotic congenital heart disease[1]

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A wide angle (60°) mechanical sector scanner producing a real-time two-dimensional echocardiogram has been used to assess the anatomy of the great arteries in 30 infants and children with cyanotic congenital heart disease. Longitudinal scans show the relations of the mitral valve and ventricular septum to the posterior great artery, and transverse scans show the spatial relations of the great arteries.

In 19 patients the echocardiographic examination was preceded by angiocardiographic diagnosis. Echocardiographic examination in 10 with complete transposition of the great arteries showed parallel great arteries; in 4 with Fallot's tetralogy, normally related great arteries with a narrow right ventricular outflow and an overriding aorta; in 4 with double outlet right ventricle, parallel great arteries, but in only 2 of these an unambiguous right ventricular origin of both great arteries; in 1 with persistent truncus arteriosus, a single artery with abnormal cusp echoes.

In 9 infants and 2 children, aged 9 and 16 years, echocardiographic examination was followed by angiocardiography. In the 9 infants the assessment of great artery size and relation by echocardiography closely correlated with that determined by angiocardiography. In the older child whose previous cardiac catheterisation without angiocardiography had suggested transposition of the great arteries, echocardiography showed normally related great arteries which were subsequently confirmed by angiocardiography. In the younger child with corrected transposition of the great arteries the echocardiographic appearance was initially misinterpreted as normally related great arteries.

Two-dimensional echocardiography, because of its capacity to display the anatomy of the ventricular outflow tracts, permits better planning of the subsequent cardiac catheterisation and angiocardiography in children with cyanotic congenital heart disease.

The findings of time-position echocardiography in transposition of the great arteries (Dillon *et al.*, 1973; Gramiak *et al.*, 1973), double outlet right ventricle (Chesler *et al.*, 1971), persistent truncus arteriosus (Chung *et al.*, 1973a), Fallot's tetralogy (Chung *et al.*, 1973b), total anomalous pulmonary venous drainage (Paquet and Gutgesell, 1975), and in cyanotic newborn infants (Godman *et al.*, 1974) have been reported. To increase the information available from echocardiography two-dimensional real-time scanning systems have recently been introduced and have proved of value in cyanotic congenital heart disease (Sahn *et al.*, 1974; Henry *et al.*, 1975; Maron *et al.*, 1975).

A wide angle (60°) mechanical sector scanner producing two-dimensional echocardiograms (Shaw *et al.*, 1976) has been used to assess great artery anatomy in infants and children with cyanotic congenital heart disease. The wide angle swept by the single element of this scanner displays simultaneously both ventricular outflow tracts. In making a preliminary report on this aspect of its clinical application we now describe and assess the results obtained in two groups of infants and children in whom the definitive diagnosis was made by cardiac catheterisation and angiocardiography.

Subjects and methods

Thirty patients with cyanotic congenital heart disease were studied. In 19 with known anomalies of the origin of the great arteries the diagnosis of

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complete transposition of the great arteries (10), double outlet right ventricle (4), Fallot's tetralogy (4), or persistent truncus arteriosus (1) had been made by angiocardiography; the age range was from 4 weeks to 16 years.

In 11 patients echocardiographic assessment of great artery size and position was made before elucidation of the abnormality by angiocardiography; the age range was 3 days to 16 years.

The ultrasonic equipment used was a mechanical 60° sector scanner (Shaw *et al.*, 1976) incorporating later developments (Houston *et al.*, 1977). In the initial part of the study a 2·5 MHz 12·5 mm diameter transducer was used but when a 5·0 MHz 6 mm diameter transducer became available it was used where appropriate. All illustrations in this report were obtained as still frame photographs from the television monitor. The convention adopted in transverse views is that the patient's left is to the right of the illustration, anterior being upwards.

The scanning planes employed were longitudinal and transverse as previously described (Houston *et al.*, 1977). The initial approach was, where possible, to obtain a longitudinal section through the great artery continuous with the anterior mitral leaflet and to determine its relation to the ventricular septum. A transverse scan was then obtained through this great artery and an attempt made to display a normal right ventricular outflow and main pulmonary artery crossing in front. In the absence of this normal relation the scanning plane was adjusted in an attempt to show the adjacent circular spaces characteristic of the parallel vessels in transposition of the great arteries (King *et al.*, 1973; Henry *et al.*, 1975); to confirm that such a circular space represented a great artery the semilunar valve echo was sought. In complex abnormalities where there was no mitral leaflet continuity with the posterior artery, the technique was modified with the intention of locating the ventricular septum and great arteries.

Results

COMPLETE TRANSPOSITION OF THE GREAT ARTERIES

In all 10 patients with complete transposition of the great arteries a high transverse scan showed two circular spaces (Fig. 1) which were confirmed as representing great arteries by the demonstration of central linear cusp echoes in diastole. It was not possible to display both great arteries at valve level in a single transverse scan in 3 of the 10 patients (Fig. 2). These illustrations were obtained with the scanner directly transverse and tilted to carry out a headwards sweep as with time-position echocardiography. In Fig. 2a a small posterior vessel, the pulmonary artery, is apparent. As the scanning plane passes upwards (Fig. 2b) the pulmonary cusp echoes are lost and a larger anterior vessel, with central cusp echoes, appears to the right; this indicates that the valve of the anterior vessel lies to the right and superior to the posterior one. The posterior vessel appears to give rise to an elongated transverse echo-free space passing posterior to the anterior artery (Fig. 2b and c). We consider that this represents the bifurcation of the pulmonary artery and confirms the identity of the posterior vessel. Definite evidence of branching of the posterior great artery was noted in 4 of the 10 patients. In all 10 the echocardiographic spatial relations were found to correspond to those determined by angiocardiography.

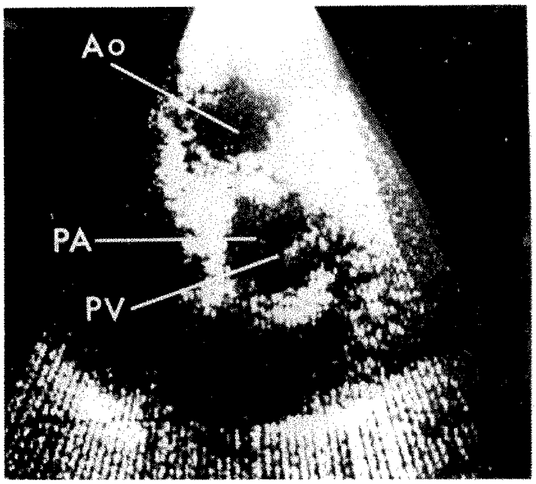

Fig. 1 *High transverse scan from an 8-day-old infant using the 5 MHz transducer. Both great arteries appear as circular echo-free spaces in systole. The aorta (Ao) lies anterior to and to the right of the pulmonary artery (PA), showing the typical configuration of the great arteries in cases of complete transposition of the great arteries. The pulmonary valve cusps (PV) are shown in the closed position in diastole.*

DOUBLE OUTLET RIGHT VENTRICLE

The 4 patients with double outlet right ventricle had echocardiographic evidence of two parallel vessels in the transverse scan. When the posterior great artery and the ventricular septum were viewed simultaneously their relation was seen to vary throughout the heart cycle, the septum moving posteriorly with respect to the great artery root during systole. The diastolic position was considered to give the best indication of the relation of the great

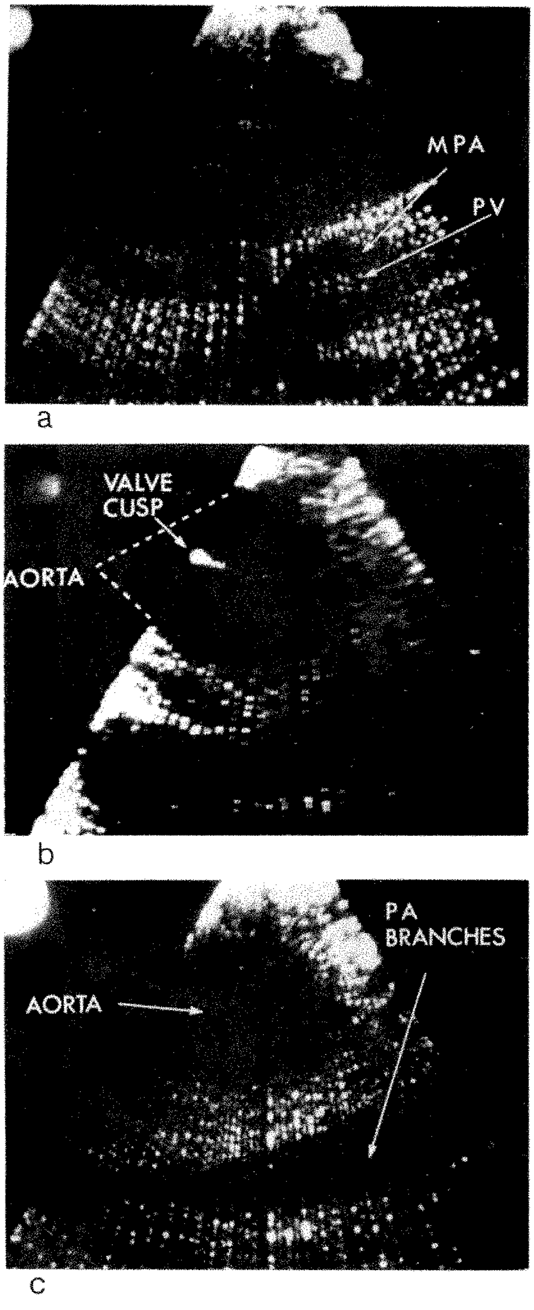

Fig. 2 *High transverse scans from a patient with complete transposition of the great arteries and pulmonary artery hypoplasia obtained as the scanning plane is tilted superiorly from (a) the level of the pulmonary valve (PV), to (b) the aortic valve, and to (c) a supravalvar level. The light in the upper left of the picture indicates the onset of the QRS complex, i.e. end-diastole.*

arteries to the ventricles. This confirmed that both arteries arose from the same ventricle in 2 cases. In the other 2, less than one-and-a-half vessels appeared to arise from the right ventricle. Longitudinal scans showed an abnormal relation between the anterior mitral leaflet and the posterior artery in 1 patient from each of these pairs; mitral-semilunar valve continuity was interrupted by intervening conal tissue.

PERSISTENT TRUNCUS ARTERIOSUS

The one patient with persistent truncus arteriosus had a single large anterior vessel (Fig. 3) overriding the ventricular septum. Within this vessel a double central echo and several eccentric echoes were seen, representing the abnormal truncal valve cusps.

FALLOT'S TETRALOGY

In the 4 patients with tetralogy a high transverse scan confirmed normally related great arteries. Three of these showed overriding of the aorta on longitudinal scan (Fig. 4). The fourth showed no overriding in diastole but the aorta and ventricular septum moved asynchronously, the septum being posterior to the anterior wall of the aorta in systole.

ECHOCARDIOGRAPHY BEFORE ANGIOCARDIOGRAPHY

The Table shows the data on the 11 cyanotic patients (including 9 infants) in whom an echocardiographic assessment of great artery anatomy was made before the elucidation of the anomaly by

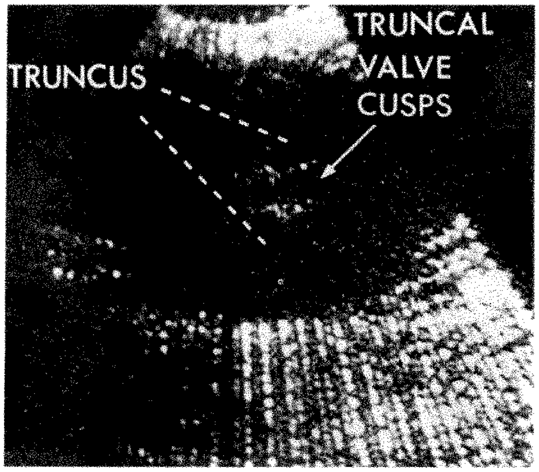

Fig. 3 *Transverse scan from the patient with persistent truncus arteriosus at the level of the truncal valve cusps.*

angiocardiography. In all 9 infants the echocardiographic assessment of great artery size and relation showed close correlation with the angiocardiographic findings. In 2 of the 4 patients with complete transposition of the great arteries, branching of the posterior artery confirmed that it was the pulmonary artery. The 16-year-old patient appeared to have normally related great arteries with a narrow right ventricular outflow and main pulmonary artery. The diagnosis of transposition of the great arteries with tricuspid atresia had been made at a previous cardiac catheterisation but because of arrhythmia no angiocardiogram had been obtained. Angiocardiography performed subsequent to the echocardiographic examination confirmed that he had normally related great arteries. An incorrect diagnosis of normally related great arteries with a narrow outflow was made in the 9-year-old child with corrected transposition. Review of the videotape recording showed that the anterior wall of the anterior left vessel had been misinterpreted as a thick immobile pulmonary valve; failure to recognise the semilunar cusp echo posterior to this caused the diagnostic error.

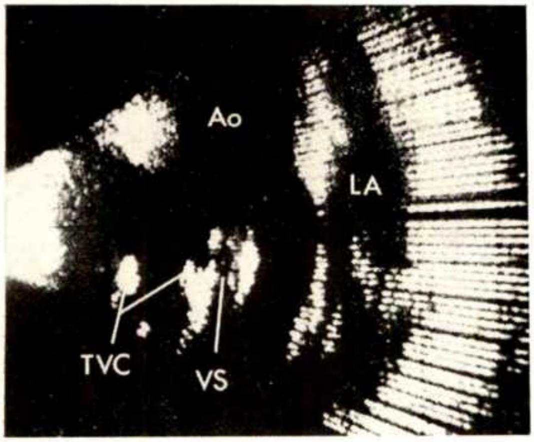

Fig. 4 *Longitudinal scan from a patient with Fallot's tetralogy showing the aorta (Ao) overriding the ventricular septum (VS); LA, left atrium; TVC, tricuspid valve cusps.*

Table *Echocardiographic assessment of the anatomy of the great arteries compared with subsequent angiographic findings*

Age	*Transducer (MHz)*	*Echocardiogram*	*Angiocardiogram*
3 d	5·0	CTGA	CTGA
8 d	5·0	CTGA	CTGA
10 d	5·0	CTGA	CTGA
6 w	2·5	Normal relations; narrow RVO and MPA	Hypoplastic RV and RVO
6 w	2·5	CTGA; narrow MPA	CTGA; hypoplastic MPA
2 m	2·5	Normal relations; wide RVO and MPA	TAPVD
4 m	2·5	Normal relations; narrow RVO and MPA	Primitive ventricle with outflow chamber
6 m	2·5	Overriding aorta; narrow RVO	Fallot's tetralogy
10 m	2·5	Overriding aorta; narrow RVO	Fallot's tetralogy
9 y	2·5	Normal relations; narrow RVO	Corrected TGA
16 y	2·5	Normal relations; narrow RVO and MPA	Primitive ventricle with outflow chamber; normally related arteries

CTGA, complete transposition of the great arteries; RVO, right ventricular outflow; MPA, main pulmonary artery; RV, right ventricle; TAPVD, total anomalous pulmonary venous drainage.

Discussion

Time - position echocardiography allows exact measurement of the distances between structures along the axis of the ultrasound beam. The determination of the relations of different structures not lying along a single beam is dependent on the operator's assessment of small changes he makes in transducer angulation; the technique is difficult, particularly when it is applied to the rapidly beating heart of a restless infant. Two-dimensional echocardiography allows exact determination of the relation of structures, thus facilitating the assessment of great artery anatomy. Other workers who have reported on the use of real-time two-dimensional echocardiography in the assessment of great artery anomalies have concluded that the method is of diagnostic value (Sahn *et al.*, 1974; Henry *et al.*, 1975; Maron *et al.*, 1975). There were some differences between their techniques and their findings in normal high transverse scans; their experience and ours have been discussed elsewhere (Houston *et al.*, 1977). We have found that a high transverse scan can show the aortic origin as a circular space with a central diastolic cusp echo, and the pulmonary artery either in the same manner when the great arteries are parallel, or as an anterior crescentic space representing the right ventricular outflow and main pulmonary artery crossing in the normal way.

In the tetralogy of Fallot or other conditions in which there are normally related great arteries the circular aorta and crescentic right ventricular outflow and main pulmonary outflow are recognised. In complete transposition of the great arteries the diagnosis is suggested by the abnormal relation of the great arteries shown by echocardiography as two echo-free circles which represent the vessels lying parallel at their origin; it is not dependent upon the separate identification of the aorta and the pulmonary artery. If, in some of the rarer types of transposition of the great arteries (Van Praagh, 1973), there should be any diagnostic difficulty it may be important to show branching of an artery which can thus be positively identified as the pulmonary artery. A problem is likely to arise when only one artery can be viewed in transverse section and no right ventricular outflow or other artery is visible, making a differential diagnosis between persistent truncus arteriosus and pulmonary atresia difficult. The abnormal eccentric cusp echoes reported by Sahn *et al.* (1974) and confirmed in our patient would be an important feature in the positive diagnosis of persistent truncus. For the diagnosis of double outflow right ventricle as defined by Lev *et al.* (1972) more than one-and-a-half great arteries should arise from the right ventricle. Echocardiographic examination of our patients showed that the relation of the great arteries to the ventricular septum varied throughout the cardiac cycle. We considered that the position in diastole was likely to show the closest agreement with findings at necropsy or operation and we used this in our assessment of their relation. In 2 of our patients more than half of one great artery appeared to be posterior to the septum, the inferior margin of the ventricular septal defect being used in this assessment. Subsequent review of the material has led to the suggestion that the superior and lateral margins of the septal defect may have been posterior to both great arteries. Chesler *et al.* (1971) with echocardiography showed mitral-semilunar valve discontinuity in double outlet right ventricle, whereas Cameron *et al.* (1976) found continuity in a minority of cases at necropsy. Two of our patients showed mitral-semilunar valve continuity and one of these on echocardiography also failed to satisfy the criterion of Lev *et al.* (1972). Thus the recognition that the ventricular septum is posterior to both arteries or that there is definite mitral-semilunar valve discontinuity is likely to be diagnostic of double outlet right ventricle, but our findings suggest that failure to recognise either by echocardiography does not exclude the diagnosis.

Correct assessment of the size of the great arteries and relation was made in 10 of the 11 patients examined before angiocardiography. In the 9-year-old child with corrected transposition an incorrect echocardiographic assessment was made while scanning and without viewing the videotape recording. This has stressed the importance of reviewing the recording before giving a diagnostic opinion. Newborn infants were not included until the 5 MHz transducer became available because the 2·5 MHz transducer could not consistently provide scans of diagnostic quality.

In conclusion we believe that the results obtained from this wide angle sector scanner in the study of the size and relation of the great arteries have shown a satisfactory correlation with the angiographic diagnosis. The extensive planar display which it provides makes it particularly suited to the exploratory role which the diagnosis of complex congenital malformations demands, and in this respect more effective than the linear display to which time-position echocardiography is confined. When it is used in the planning of the cardiac catheterisation and angiocardiography of infants with cyanotic congenital heart disease we are convinced that these investigations can be performed more expeditiously.

We are indebted to Mr. A. Shaw, B.Sc., who directed the development of the scanning equipment, and to Mr. D. J. Wheatly, F.R.C.S., who initiated its clinical application. We acknowledge the help we have received from Dr. E. M. Sweet, Dr. M. McNair, and Miss J. L. McLardy of the Radiology Department of the Royal Hospital for Sick Children, Glasgow.

References

Cameron, A. H., Acerete, F., Quero, M., and Castro, M. C. (1976). Double outlet right ventricle. Study of 27 cases. *British Heart Journal*, **38**, 1124–1132.

Chesler, E., Joffe, H. S., Beck, W., and Schrire, V. (1971). Echocardiographic recognition of mitral-semilunar valve discontinuity. An aid to the diagnosis of origin of both great vessels from the right ventricle. *Circulation*, **43**, 725–732.

Chung, K. J., Alexson, C. G., Manning, J. A., and Gramiak, R. (1973a). Echocardiography in truncus arteriosus. The value of pulmonic valve detection. *Circulation*, **48**, 281–286.

Chung, K. J., Nanda, N. C., Manning, J. A., and Gramiak, R. (1973b). Echocardiographic findings in tetralogy of Fallot. *American Journal of Cardiology*, **31**, 126.

Dillon, J. C., Feigenbaum, H., Konecke, L. L., Keutel, J., Hurwitz, R. A., Davis, R. H., and Chang, S. (1973). Echocardiographic manifestations of D-transposition of the great vessels. *American Journal of Cardiology*, **32**, 74–78.

Godman, M. J., Tham, P., and Kidd, B. S. L. (1974). Echocardiography in the evaluation of the cyanotic newborn infant. *British Heart Journal*, **36**, 154–166.

Gramiak, R., Chung, K. J., Nanda, N., and Manning, J. (1973). Echocardiographic diagnosis of transposition of the great vessels. *Radiology*, **106**, 187–189.

Henry, W. L., Maron, B. J., Griffith, J. M., Redwood, D. R., and Epstein, S. E. (1975). Differential diagnosis of anomalies of the great arteries by real-time two-dimensional echocardiography. *Circulation*, **51**, 283–291.

Houston, A. B., Gregory, N. L., Shaw, A., Wheatley, D. J., and Coleman, E. N. (1977). Two-dimensional echocardiography with a wide angle (60°) sector scanner. *British Heart Journal*, **39**, 1071–1075.

King, D. L., Steeg, C. N., and Ellis, K. (1973). Demonstration of transposition of the great arteries by cardiac ultrasonography. *Radiology*, **107**, 181–186.

Lev, M., Bharati, S., Meng, C. C. L., Liberthson, R. R., Paul, M. H., and Idriss, F. (1972). A concept of double-outlet right ventricle. *Journal of Thoracic and Cardiovascular Surgery*, **64**, 271–281.

Maron, B. J., Henry, W. L., Griffith, J. M., Freedom, R. M., Kelly, D. T., and Epstein, S. E. (1975). Identification of congenital malformations of the great arteries in infants by real-time two-dimensional echocardiography. *Circulation*, **52**, 671–677.

Paquet, M., and Gutgesell, H. (1975). Echocardiographic features of total anomalous pulmonary venous connection. *Circulation*, **51**, 599–605.

Sahn, D. J., Terry, R., O'Rourke, R., Leopold, G., and Friedman, W. F. (1974). Multiple crystal cross-sectional echocardiography in the diagnosis of cyanotic congenital heart disease. *Circulation*, **50**, 230–238.

Shaw, A., Paton, J. S., Gregory, N. L., and Wheatley, D. J. (1976). A real-time 2-dimensional ultrasonic scanner for clinical use. *Ultrasonics*, **14**, 35–40.

Van Praagh, R. (1973). Do side by side great arteries merit a special name? *American Journal of Cardiology*, **32**, 874–876.

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Aortic root and left atrial wall motion

An echocardiographic study

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The echocardiographically recorded movement of the aortic root was studied by analysing the relation between posterior aortic wall motion and other intracardiac events. The systolic anterior movement of the aortic root continued beyond aortic valve closure and in cases with mitral regurgitation began significantly earlier than in normal subjects. The diastolic rapid posterior movement began after mitral valve opening but did not occur in patients with mitral stenosis. The total amplitude of aortic root motion was increased in patients with mitral regurgitation, diminished in cases of mitral stenosis, and was normal with aortic regurgitation. In patients with atrioventricular block an abrupt posterior movement followed the P wave of the electrocardiogram irrespective of its timing in diastole. These observations correlate with the expected changes in left atrial volume during the cardiac cycle both in the normal subjects and patients with heart disease.

The results support the hypothesis that phasic changes in left atrial dimension are largely responsible for the echocardiographically observed movement of the aortic root and indicate a potential role for echocardiography in the analysis of left atrial events.

Echocardiographic examination of the aortic root and aortic valve has proved to be valuable in the assessment of patients with a variety of disorders including aortic valve disease (Gramiak and Shah, 1970; Feizi *et al.*, 1974), dissecting aneurysm of the ascending aorta (Nanda *et al.*, 1973), and supravalvar aortic stenosis (Bolen *et al.*, 1975). At the same time it is possible to make an estimate of left atrial dimension (Hirata *et al.*, 1969; tenCate *et al.*, 1974) which is helpful in cases of mitral stenosis and other conditions in which left atrial dilatation is a feature. Recently attention has been directed to observation of the movement of the aortic root and in particular the amplitude of this movement. It has been shown that this may vary considerably between patients (Gramiak and Shah, 1968), and a relation between the amplitude and stroke volume has been reported (Pratt *et al.*, 1976). This observation was based on the assumption that the motion of the aortic root is the result of the ejection phase of left ventricular contraction. However, combined angiocardiographic and echocardiographic studies have suggested that changes in left atrial volume may be the major determinant of aortic root motion (Strunk *et al.*, 1976a). The relation of posterior aortic wall movement to other cardiac events has not been established.

As a result of observations made on echocardiograms obtained by the routine diagnostic service at the London Hospital we also gained the impression that the motion of the aortic root is largely the result of movement of the left atrial wall and phasic changes in left atrial dimension. This implies that aortic root motion is not an index of left ventricular function but might provide useful information about left atrial events in patients with heart disease. A prospective study using echocardiography and phonocardiography was, therefore, undertaken to establish the determinants of aortic root motion throughout the cardiac cycle.

Subjects and methods

Studies were performed on 12 normal subjects and 30 patients with heart disease. The latter included 10 patients with isolated mitral stenosis, 11 with pure mitral regurgitation, 7 with free aortic regurgitation, and 2 with atrioventricular block. All the patients had characteristic clinical, electrocardiographic, radiographic, and echocardiographic findings associated with their cardiac lesion.

Echocardiograms were obtained using a Smith Kline Ekoline 20 ultra-sound recorder with a 2·25 MHz focussed transducer and a repetition rate of 1000 a second. The output of the Ekoline 20 was interfaced with a Cambridge multichannel

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photographic recorder allowing simultaneous recording of the echogram, electrocardiogram (lead II) and phonocardiogram at a paper speed of 100 mm a second. Phonocardiograms were obtained using a piezoelectric crystal microphone placed either at the cardiac apex or at the left sternal edge in the second interspace.

The mitral valve echogram was recorded in the conventional way, with care taken to ensure that both cusps were clearly seen during opening of the valve. Similarly for the aortic valve at least two cusps were visualised at the time of separation. The aortic root and left atrium were then examined ensuring clear delineation of the posterior aortic wall and posterior left atrial wall throughout the cardiac cycle. To help standardise the transducer position, elements of the aortic valve cusps were always included within the aortic lumen when recording the aortic root and left atrial echogram.

The following time intervals and amplitudes were measured:

Q—MC (ms)—onset of Q wave to mitral valve closure;
Q—AVO (ms)—onset of Q wave to aortic cusp separation;
Q—peak AVO (ms)—Q wave to maximum separation of aortic cusps;
A_2—MVO (ms)—aortic component of second heart sound (or aortic cusp apposition) to mitral cusp separation;
A_2—peak MVO (ms)—aortic valve closure to maximum separation of mitral valve cusps;
Q—start ARM (ms)—Q wave to start of anterior motion of aortic root;
A_2—peak ARM (ms) valve closure to most anterior position of aortic root;
Amp ARM (mm)—amplitude of aortic root motion;
LA max (mm)—maximum left atrial dimension.

All measurements given were calculated as the average of at least five cardiac cycles. Time intervals were measured to the nearest 5 ms. The differences in the values found for these variables in the patient groups when compared to the normal subjects were analysed using Student's unpaired t test.

Results

(a) NORMAL SUBJECTS

The typical pattern of aortic root motion in the normal subjects is shown in Fig. 1. During ventricular systole there is an anterior movement followed in the early part of diastole by a posterior motion. In later diastole little further movement is seen until after the P wave of the electrocardiogram though in some subjects a definite slow anterior deflection is seen. Following the P wave a rapid posterior movement occurs, which usually consists of two distinct components with a brief anterior movement separating the two. The details of the timing of the cardiac events are shown in the Table. In all normal subjects the anterior systolic motion of the aortic root did not begin until after the onset of aortic valve opening occurring with a mean delay of 121 ms after Q. In 3 cases it was delayed by up to 14 ms after peak opening of the aortic valve; in one subject its onset was synchronous with peak aortic valve opening and in the remainder it preceded peak aortic opening. In all subjects the anterior motion continued beyond aortic valve closure and the onset of mitral valve opening but was always completed before peak opening of the mitral valve had occurred. In some cases a transient posterior movement occurred synchronous with aortic valve closure. The first component of the presystolic posterior movement always followed the P wave of the electrocardiogram and was completed before mitral valve closure. The second component invariably occurred after mitral valve closure mainly occupying the period of isovolumic ventricular contraction. In between these two presystolic posterior movements a small anterior displacement is seen (Fig. 1).

The mean amplitude of posterior aortic wall motion for the normal group was 11·6 mm (SEM = 0·4). The mean left atrial dimension at its maximum point was 31·3 mm (SEM = 1·2).

(b) MITRAL STENOSIS

In all patients with mitral stenosis a distinct deviation from the normal pattern of aortic root motion was seen (Fig. 2). During ventricular systole the aortic root moved anteriorly with a temporal relation to aortic valve opening similar to that in the normal subjects. However, mitral valve opening occurred earlier though this difference was not statistically significant. The peak of the anterior movement of the aortic root also occurred earlier but this too was not statistically significant. As in the normal group this followed mitral valve opening in each patient. During the early part of diastole the rapid posterior movement seen in the normal subjects was replaced by a slower motion which continued throughout the length of diastole, thus replacing the plateau in late diastole found normally. Since all the patients in this group had atrial fibrillation the posterior motion associated with atrial systole in the normal subjects was not seen. Closure of the mitral valve was significantly delayed in the patients with mitral stenosis. The relation of aortic root movement to other cardiac events is shown in the Table.

The mean amplitude of posterior aortic wall motion (Fig. 3) was 7·8 mm (SEM = 0·5) which was significantly less than for the normal subjects (P < 0·001). Maximum left atrial diameter was 47·7 mm (SEM = 2·0) which was significantly greater than the normal group (Fig. 4).

(c) MITRAL REGURGITATION

The pattern of movement of the posterior aortic wall in these patients was similar to that seen in the normal subjects (Table). However the onset of forward movement of the aortic root occurred 96 ms after Q and this was significantly earlier (P < 0·001) than in the normal group. Similarly, the interval from aortic valve closure to the maximum anterior position of the aortic root was also significantly shorter at 71 ms. The amplitude of posterior aortic wall motion was significantly greater than for the normal group (P < 0·005) and also greater than for the other patients studied (Fig. 3). The left atrial diameter (52 mm) was also significantly greater than for the normal group (Fig. 4).

(d) AORTIC REGURGITATION

In patients with aortic regurgitation forward movement of the aortic root began 122 ms after Q (Table) which was similar to the finding in the normal group but the maximum anterior position was reached significantly later (98 ms after aortic valve closure) than in the normal subjects. Opening of the mitral valve was also delayed significantly in these patients, occurring 84 ms after aortic valve closure.

The amplitude of posterior aortic wall move-

Table *Time relation of intracardiac events derived from echocardiograms and phonocardiograms*

	Q-MC	*Q-AVO*	*Q-start ARM*	*Q-pkAVO*	*A_2-MVO*	*A_2-pkARM*	*A_2-pkMVO*
Normal	58 ± 2	96 ± 3	121 ± 3	126 ± 4	61 ± 4	85 ± 2	115 ± 5
Mitral stenosis	76 ± 4 P < 0·005	103 ± 4	125 ± 6	127 ± 5	55 ± 4	74 ± 8	97 ± 6
Mitral regurgitation	63 ± 5	96 ± 4	96 ± 2 P < 0·001	120 ± 5	62 ± 4	71 ± 7 P < 0·005	117 ± 6
Aortic regurgitation	53 ± 7	87 ± 6	122 ± 4	115 ± 8	84 ± 10 P < 0·01	98 ± 9 P < 0·05	148 ± 13 P < 0·01

AVO, aortic valve opening; pkAVO, peak separation of aortic cusps; MVO, mitral valve opening; ARM, aortic root movement. Time intervals are measured in ms and are given as the mean and standard error of the mean.

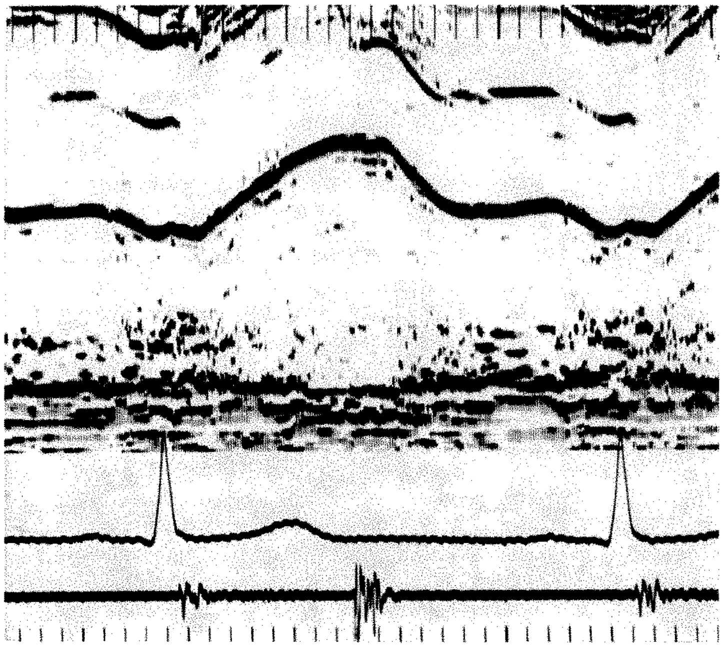

Fig. 1 *Normal left atrial and aortic root echocardiogram. The anterior systolic motion continues beyond aortic valve closure and is followed by a rapid posterior movement in early diastole. A further posterior movement follows the P wave.*

ment was 11·6 mm (SEM = 1·1) and the left atrial diameter was 33·7 mm (SEM = 1·8) both of which did not differ significantly from the normal values (Fig. 3 and 4).

(e) ATRIOVENTRICULAR BLOCK

Two patients with complete atrioventricular block were investigated to examine the effect of atrial systole on the movement of the posterior aortic wall. Detailed measurements were not made in these cases. The pattern of aortic root movement seen is shown in Fig. 5. Irrespective of its timing in diastole the P wave of the electrocardiogram was followed by a posterior movement of the aortic wall which then maintained its new position with only minor variation for the rest of diastole.

Discussion

Angiocardiography and left atrial echocardiography show that considerable changes in left atrial anteroposterior dimension occur throughout the cardiac cycle (Strunk *et al.*, 1976a). Since the posterior wall of the left atrium is fixed in position by its attachment to the pulmonary veins, virtually all of this dimension change is the result of movement of the anterior wall of the atrium which is attached to the aortic root and posterior aortic wall. This motion of the last may, therefore, be the result of phasic changes in left atrial volume or alternatively may be the result of an isovolumic change in left atrial shape. In the latter case a reduction in left atrial

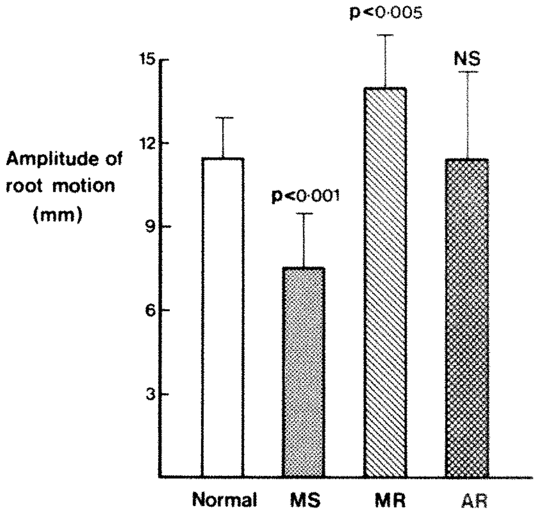

Fig. 3 *Amplitude of aortic root motion in the four groups studied. Bars indicate standard error of the mean.*

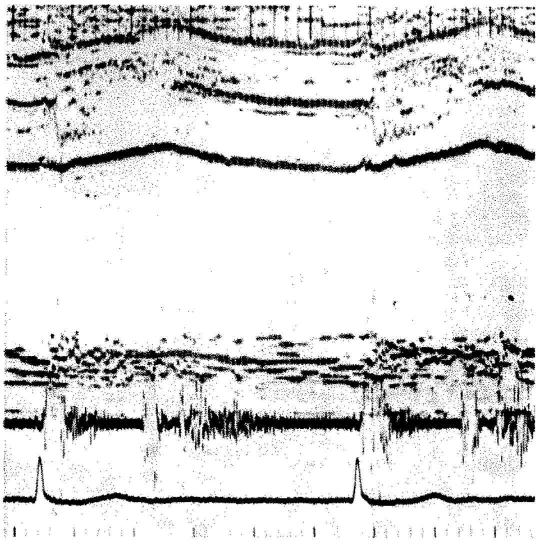

Fig. 2 *Left atrial and aortic root echocardiogram in mitral stenosis. The amplitude of root movement is reduced and the rapid early diastolic posterior movement is replaced by a slower motion continuing throughout diastole.*

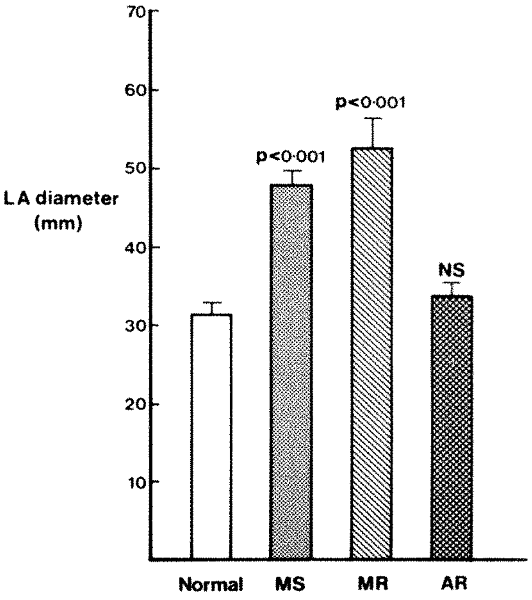

Fig. 4 *Left atrial diameter in the four groups studied. Bars indicate standard error of the mean.*

anteroposterior dimension must be accompanied by an increase in dimension in some other plane. While it is accepted that the diameter of the aortic root changes only slightly through the cardiac cycle except in patients with free aortic regurgitation (Arcilla *et al.*, 1961) it has nevertheless been suggested that aortic root motion is the result of left ventricular systole and especially the ejection phase (Pratt *et al.*, 1976). This concept has been extended by a report apparently indicating that the amplitude of aortic posterior wall motion is a useful indicator of left ventricular performance and may even be used to quantify the stroke volume (Pratt *et al.*, 1976). If the concept is correct it would suggest that the left atrial dimension changes in a passive manner as a result of atrial isovolumic shape alterations related to displacement of other cardiac structures, in particular the aorta; further, these shape changes would be determined by the function of the left ventricle. The results of the studies reported here, however, cast serious doubts on the validity of this concept.

In the first instance no increase in the amplitude of aortic posterior wall motion could be shown in patients with free aortic regurgitation, despite the large stroke volume usually present in these cases (Miller *et al.*, 1965). Secondly, in patients with gross mitral regurgitation the amplitude of movement was increased though forward flow into the aorta would not be expected to be raised (Miller *et al.*, 1965). Thirdly, atrial systole distinctly alters the position of the aortic root causing a reduction in the left atrial dimension.

Further evidence suggesting that atrial volume is the major determinant of aortic root movement is obtained from the analysis of the temporal relations of this motion to other intracardiac events. The anterior movement which occurs during ventricular systole always continues beyond aortic valve closure even in patients with aortic regurgitation and cannot, therefore, be the result of ventricular contraction. It is always completed after the mitral valve has started to open but before peak separation of the cusps has occurred, this relation being maintained in the patients with aortic regurgitation in whom mitral valve opening is delayed. It is, therefore, compatible with an increase in left atrial dimension during systole reflecting the enlarging volume of that chamber when the mitral valve is closed. After mitral cusp separation begins left ventricular filling occurs, the left atrial dimension decreases and the aortic root moves rapidly posteriorly. In patients with mitral stenosis the rapid ventricular filling phase is lost and this is reflected by a more gradual posterior motion of the aortic root and reduction in left atrial dimension. This can be related to the severity of the mitral stenosis (Strunk *et al.*, 1976b). Furthermore, this movement continues throughout the length of diastole consistent with the prolongation of left ventricular filling and altered pattern of mitral valve flow (Kalmanson *et al.*, 1976).

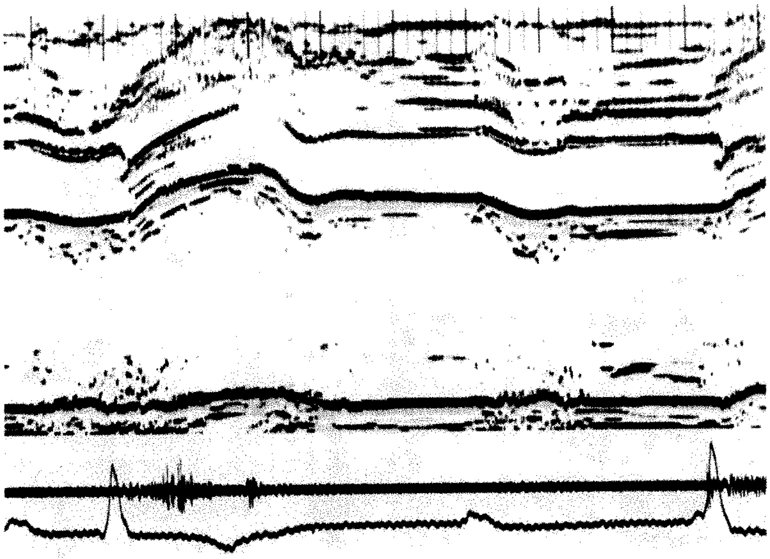

Fig. 5 *Left atrial and aortic root echocardiogram in atrioventricular block. The P wave is followed by a posterior movement of the aortic root irrespective of its timing in diastole.*

In sinus rhythm the posterior movement of the aortic root during atrial systole ends with mitral valve closure but during isovolumic ventricular systole a further small posterior motion occurs. This clearly cannot relate to ventricular ejection but may be the result of a change in left atrial shape as the mitral valve moves in a posterior and superior direction away from the apex of the left ventricle (Strunk *et al.*, 1976a). This small change in left atrial dimension during isovolumic ventricular contraction is, therefore, the only event that cannot be explained on the basis of atrial volume but rather as a consequence of a change in left atrial shape.

These results indicate that movement of the posterior aortic wall is primarily determined by left atrial events rather than the effects of left ventricular systole. This finding has immediate practical significance since it implies that observation of posterior aortic wall (or more correctly left atrial wall) motion cannot be used to assess the performance of the left ventricle. In particular the apparent relation between stroke volume and amplitude of aortic root movement does not apply in the presence of mitral or aortic regurgitation. However, left atrial echocardiography can provide information related to left atrial volume and specifically left atrial anteroposterior dimension.

In mitral stenosis the left atrial dimension changes slowly during diastole. The change in dimension is also considerably smaller than normal as a result of reduced posterior aortic wall motion. This may reflect a diminished left atrial blood flow but could also result from reduced left atrial compliance. In addition the left atrial volume is increased so that small changes in dimension may be associated with normal changes in volume. In patients with mitral regurgitation even larger left atrial dimensions are found but the amplitude of left atrial wall movement, and therefore the amplitude of variation in dimension, were also increased. This results from the large phasic changes in left atrial volume expected in this condition.

Although the mitral valve echogram can be used as an index of the severity of mitral stenosis (Gustafson, 1967), mitral regurgitation has proved more difficult to evaluate. Further analysis of left atrial echograms based on measurements of phasic left atrial dimensions may yield additional information of value in this area. In particular the functional data can be expected to serve as an adjunct to the predominantly anatomical information available from the mitral echogram.

References

Arcilla, R. A., Agustsson, M., Steiger, Z., and Gasul, B. M. (1961). An angiocardiographic sign of aortic regurgitation. *Circulation,* **23,** 269–278.

Bolen, J. L., Popp, R. L., and French, J. W. (1975). Echocardiographic features of supravalvular aortic stenosis. *Circulation,* **52,** 817–822.

Feizi, O., Symons, C., and Yacoub, M. (1974). Echocardiography of the aortic valve. *British Heart Journal,* **36,** 341–351.

Gramiak, R., and Shah, P. M. (1968). Echocardiography of the aortic root. *Investigative Radiology,* **3,** 356–366.

Gramiak, R., and Shah, P. M. (1970). Echocardiography of the normal and diseased aortic valve. *Radiology,* **96,** 1–8.

Gustafson, A. (1967). Correlation between ultrasoundcardiography, hemodynamics and surgical findings in mitral stenosis. *American Journal of Cardiology,* **19,** 32–41.

Hirata, T., Wolfe, S. B., Popp, R. L., Helmen, C. H., and Feigenbaum, H. (1969). Estimation of left atrial size using ultrasound. *American Heart Journal,* **78,** 43–52.

Kalmanson, D., Veyrat, C., Bernier, A., Witchitz, S., and Chiche, P. (1976). Opening snap and isovolumic relaxation period in relation to mitral valve flow in patients with mitral stenosis. *British Heart Journal,* **38,** 135–146.

Miller, G. A. H., Kirklin, J. W., and Swan, H. J. C. (1965). Myocardial function and left ventricular volumes in acquired valvular insufficiency. *Circulation,* **31,** 374–384.

Nanda, N. C., Gramiak, R., and Shah, P. M. (1973). Diagnosis of aortic root dissection by echocardiography. *Circulation,* **48,** 506–513.

Pratt, R. C., Parisi, A. F., Harrington, J. J., and Sasahara, A. A. (1976). The influence of left ventricular stroke volume on aortic root motion. *Circulation,* **53,** 947–953.

Strunk, B. L., Fitzgerald, J. W., Lipton, M., Popp, R. L., and Barry, W. H. (1976a). The posterior aortic wall echocardiogram. *Circulation,* **54,** 744–750.

Strunk, B. L., Fitzgerald, J. W., Alderman, E. L., Popp, R. L., and Barry, W. H. (1976b). The value of the left atrial echogram in quantitating the severity of mitral regurgitation and mitral stenosis (abstract). *American Journal of Cardiology,* **37,** 175.

tenCate, F. J., Kloster, F. E., van Dorp, W. G., Meester, G. T., and Roelandt, J. (1974). Dimension and volumes of left atrium and ventricle determined by single beam echocardiography. *British Heart Journal,* **36,** 737–746.

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Assessment of ventricular elements of mitral valve by left ventriculography

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In the left ventriculogram in the right anterior oblique projection the plane of the mitral valve is seen in profile and the papillary muscle shadows are outlined. The distance from the middle of the papillary muscles to the plane of the mitral valve during systole was used to assess the average length of the chordae tendineae, and the area of the papillary muscle shadows was measured as an index of hypertrophy in a series of hearts with mitral valve disease. Valvar mitral stenosis is characterised by slight reduction in the length of chordae tendineae and more hypertrophy of the papillary muscles, while in subvalvar mitral stenosis there is more shortening of the chordae tendineae and less papillary muscle hypertrophy. Valvotomy may lengthen the chordae tendineae in subvalvar mitral stenosis. In rheumatic mitral regurgitation length of chordae tendineae and papillary muscle size were normal. The measurements were not useful in assessing non-rheumatic mitral regurgitation.

Clinical evaluation of the mitral valve must take into consideration the functional activity of each element that participates in valve movement. Some information can be obtained from physical examination and from the electrocardiogram and echocardiogram, but assessment of the morphology and the movement of the valve and its subvalvar elements requires left ventriculography. In the right anterior oblique projection the ostium of the left ventricle, the mitral valve, and the supporting papillary muscles are seen in profile (Ross and Criley, 1964); in the left anterior oblique projection the anterior (aortic) leaflet is in profile (Bittar and Sosa, 1972).

We describe here procedures developed to assess (a) the average length of the chordae tendineae and (b) papillary muscle hypertrophy in mitral valve disease. On the left ventriculogram in the right anterior oblique projection, the distance from the middle of the papillary muscles to the plane of the mitral valve was used to represent chordae tendineae length and the area of the papillary muscles was measured by planimetry to assess papillary muscle hypertrophy. Both measurements were related to the end-systolic longitudinal axis of the left ventricle and expressed as the chordae tendineae and papillary muscle hypertrophy indices.

A close relation was found between the chordae tendineae index and the measured length of chordae tendineae from the surgical specimens of mitral stenosis. Both the chordae tendineae and the papillary muscle hypertrophy index levels are larger with valvar mitral stenosis than with subvalvar mitral stenosis. When these indices are measured in patients with restenosis of the mitral valve after valvotomy, additional insight into the pathophysiology of mitral stenosis is obtained. The indices are not useful in assessing the pathology of mitral regurgitation alone or in combination with mitral stenosis.

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Methods

Records of cardiac catheterisation and cineangiography from consecutive patients with mitral valve disease studied at Guy's Hospital (London) and at Jackson Memorial Hospital (University of Miami) provided the material for this investigation. The 'normals' were matched for age as closely as possible with the study group and were subjects who were catheterised to exclude organic heart disease and found to have no haemodynamic or cineangiographic abnormality. The stroke index was determined by standard procedures.

Left ventriculograms were obtained at Guy's Hospital with a Siemens radiographic generator, Arriflex cinecamera, and Kodak XX film exposed at 30 frames per second, and at the University of Miami with a Picker generator using grid pulsing fluorographic control and Kodak Shellburst cineangiographic film exposed at 60 frames per second.

At Guy's the contrast medium was Hypaque 85 per cent and was delivered by Talley injector; Renografin–76 (30 to 34 ml) was injected through a Gensini or pigtail catheter, using a Viamonte-Hobbs injector, at the University of Miami. In both institutions, a 30° right anterior oblique position was used.

The ventriculograms were analysed using the Tage-Arno projector. Outlines of the left ventricular cavity and of the papillary muscles at end-systole were traced and the distance between the middle of the papillary muscles and the centre of the left ventricular ostium was measured. Papillary muscle area was determined by planimetric measurements of the papillary muscle shadows (Fig. 1).

Results

The distance from the middle of the papillary muscles to the left ventricular ostium and measurements of long axis of the left ventricle at end-systole in normal hearts and in hearts from patients with mitral stenosis are shown in Table 1. Differences caused by variations in radiographic imaging are eliminated by relating the chordal measurement to the long axis of the ventricle; the ratio was described as the chordae tendineae index.

Traces of the end-systolic left ventriculograms from a normal heart and hearts with dominantly valvar or mixed valvar and subvalvar ('subvalvar') mitral stenosis are shown in Fig. 1. The lines used for measuring chordae tendineae distance, the papillary muscle area, and the long axis of the ventricle at end-systole are illustrated. a is from a heart with subvalvar mitral stenosis, b from valvar mitral stenosis with mild aortic regurgitation, and c from a normal heart. The shorter chordae tendineae distance in subvalvar mitral stenosis is appreciated by comparing a with b or c. (The greater length of the ventricle in b results from ventricular enlargement secondary to aortic regurgitation.)

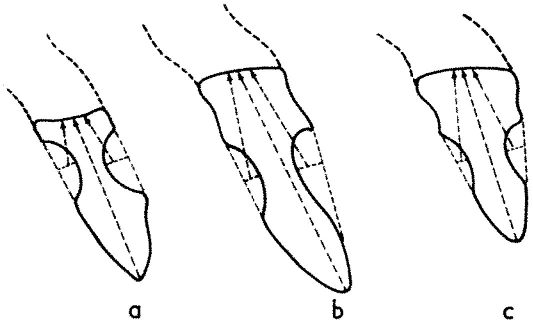

Fig. 1 *Tracing of outline of left ventricle from ventriculogram in right anterior oblique projection in (a) valvar and severe subvalvar mitral stenosis (case 5), (b) valvar mitral stenosis and mild aortic regurgitation (case 1), and (c) normal heart.*

The idea that the chordae tendineae index reflects the length of the chordae tendineae is supported by the close relation between the index and the average chordae tendineae length from 5 surgical specimens of mitral valves (Table 2). Measurements of the surgical specimens were made after suturing the annular margin of the resected valve to 'dacron' fabric that was then mounted on a wooden frame. Heavy suture material was passed through the body of the papillary muscles and the chordae tendineae were extended. Multiple measurements of the shortest and longest chordae tendineae inserted into the rough zone of the valve leaflet were averaged. Mounted valves viewed from the left atrium and from a simulated right anterior oblique projection are shown in Fig. 2. The chordae tendineae index for the anterior and posterior measurements ranged from 0·38 to 0·23 (Table 2). The lowest values for this index occurred with severe shortening of the chordae tendineae (cases 4 and 5; Fig. 1 and 2) and the higher values with longer chordae (cases 2 and 3). The specimen with the longest chordae (case 1) had low values because of the increase in length of the ventricle as a result of aortic regurgitation (trace b and Fig. 2).

Table 1 *Angiographic assessment of end-systolic length of chordae tendineae in mitral stenosis*

	Normal subjects			*Mitral stenosis*		
	Length of chordae (cm)	*Ventricular long axis (cm)*	*CTI**	*Length of chordae (cm)*	*Ventricular long axis (cm)*	*CTI**
Series						
British	3·6 ±0·2 (7)	7·5 ±0·5	0·5 ±0·03	3·1 ±0·2 (19)	7·8 ±0·3	0·40 ±0·02
U.S.A.	6·2 ±0·4 (8)	10·9 ±0·9	0·6 ±0·01	4·5 ±0·02 (45)	10·3 ±0·3	0·43 ±0·01

*CTI, chordae tendineae index (i.e. ratio between length of chordae and ventricular long axis).
Measurements expressed as mean ±standard deviation (number of hearts in parentheses).

The chordae tendineae index in 64 patients with mitral stenosis is shown in Fig. 3. Twenty-six of these were classified at operation or at necropsy as having major shortening of the chordae tendineae and were considered as subvalvar mitral stenosis; 38 had dominant valvar mitral stenosis. The chordae tendineae index for the normal hearts (0·53 ± 0·02) is significantly higher than the value for either group of mitral stenosis (P < 0·001). The value for subvalvar mitral stenosis is significantly lower than in valvar mitral stenosis (P < 0·001). In Fig. 3 triangles refer to hearts with restenosis of the mitral valve after valvotomy and will be discussed below.

In some hearts, both papillary muscle shadows are poorly outlined; these were excluded from the study. In approximately 1 out of 5 hearts with mitral stenosis, the anterior papillary muscle of the left ventricle could not be outlined; in these the measurement for the posterior papillary muscle was used. In the other hearts the areas of the anterior and posterior papillary muscles were averaged.

The papillary muscle hypertrophy index in

Table 2 *Length of chordae tendineae in mitral stenosis*

Case No.	*Left ventriculographic measurement (CTI)**		*Chordae tendineae length of surgical specimen (mm)*		*Surgeon's remarks*
	Anterior	*Posterior*	*Anterior*	*Posterior*	
1†	0·38	0·32	18	25	Valvar stenosis; chordae tendineae thickened but not fused or shortened
2	0·36	0·31	20	10	Valvar stenosis; chordae tendineae shortened and fused
3	0·34	0·31	12	15	Grossly disorganised stenosed valve; chordae tendineae shortened and fused
4	0·28	0·33	8	13	Valvar and subvalvar stenosis
5	0·25	0·23	7	6	Valvar stenosis; thickening and fusion of chordae tendineae, with resulting subvalvar stenosis
Normal	0·53		18–14‡		

*CTI, chordae tendineae index.
†Mild aortic regurgitation.
‡Chordae tendineae inserting into the rough zone of the valve leaflet (Lam *et al.*, 1970).

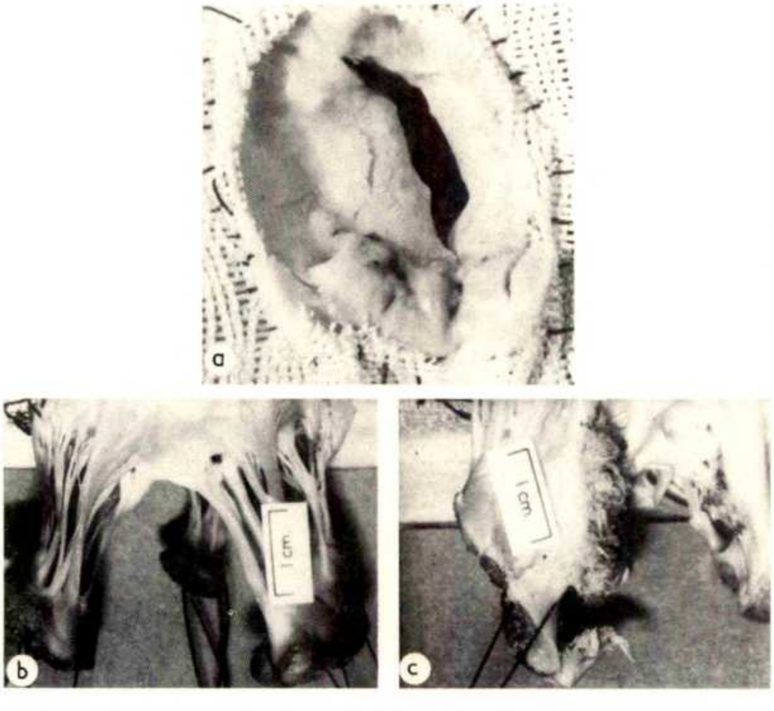

Fig. 2 *Surgical specimens of mounted valves with mitral stenosis (a) annular margins sutured to a 'dacron' support viewed from above, (b) chordae tendineae from heart of case 1 with valvar mitral stenosis, and (c) severely shortened chordae tendineae from case 5 with valvar plus subvalvar mitral stenosis. Note the villous-like Lambl's excrescences (Magarey, 1949) on the chordae tendineae and the papillary muscle.*

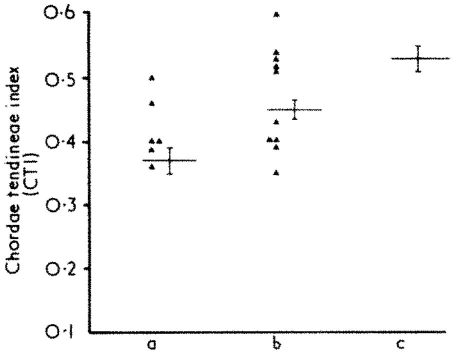

Fig. 3 *Chordae tendineae indices (CTI) in (a) 26 hearts with subvalvar mitral stenosis, (b) 38 hearts with valvar mitral stenosis, and (c) 15 normal hearts. Horizontal line represents the mean value, and vertical bar the standard error. Triangles denote hearts with restenosis after valvotomy.*

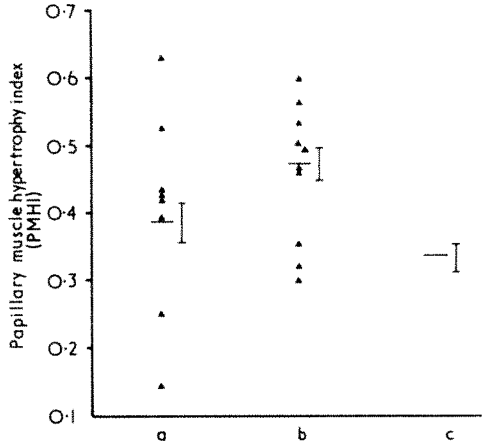

Fig. 4 *Papillary muscle hypertrophy index (PMHI) in (a) 26 hearts with subvalvar mitral stenosis, (b) 38 hearts with valvar mitral stenosis, and (c) 15 normal hearts. Horizontal line represents the mean value, and vertical bar the standard error. Triangles denote hearts with restenosis after valvotomy.*

valvar mitral stenosis is significantly higher than in the normal hearts ($P < 0{\cdot}01$), and probably higher than in subvalvar mitral stenosis ($P < 0{\cdot}05$) (Fig. 4). As in Fig. 3, triangles refer to hearts with restenosis.

Table 3 shows that the chordae tendineae index in hearts with sinus rhythm is similar to that in hearts with atrial fibrillation, even though atrial fibrillation is associated with lower stroke indices.

The angiographic indices are of limited value in rheumatic or non-rheumatic mitral regurgitation. The chordae tendineae index in 24 hearts with rheumatic mitral regurgitation of 0·48 (Table 3) is not significantly different from that in normal hearts.

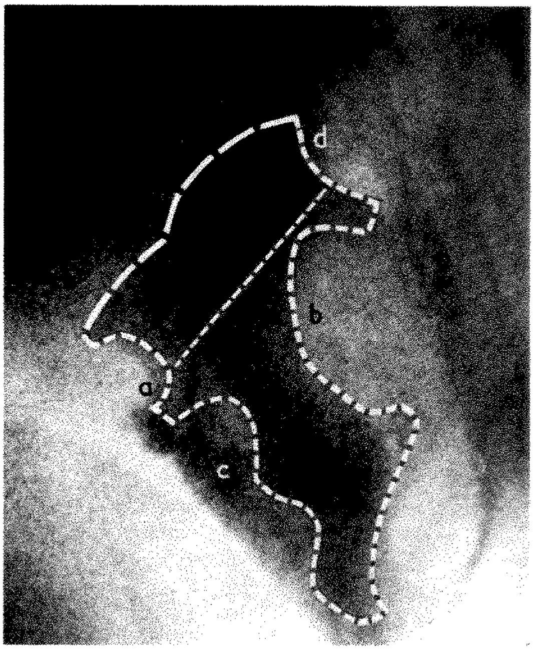

Fig. 5 *Left ventriculogram in patient with prolapsed mitral valve, showing (a) outline of left ventricular ostium, (b and c) anterior and posterior papillary muscles, and (d) prolapsed mitral valve.*

Table 3 *Chordae tendineae index in rheumatic mitral valve disease in sinus rhythm and atrial fibrillation*

	Stroke index ml/beat per m²		*CTI**	
	Sinus	*Atrial fibrillation*	*Sinus*	*Atrial fibrillation*
Mitral stenosis				
Valvar	39 ± 9 (18)	25 ± 11 (19)	0·46 ± 0·05	0·44 ± 0·09
Subvalvar	36 ± 7 (10)	25 ± 8 (15)	0·38 ± 0·09	0·36 ± 0·07
Mitral regurgitation	34 ± 11 (13)	26 ± 11 (11)	0·48 ± 0·12	0·48 ± 0·08

*CTI, chordae tendineae index.
Measurements expressed as mean ± standard deviation (number of hearts in parentheses).

With a prolapsed mitral valve, the aberrant shape and position of both leaflets of the mitral valve obscure the outline of the left ventricular ostium and the profile of the papillary muscles is often displaced or deformed (Fig. 5).

Discussion

Post-rheumatic mitral stenosis is initiated by endothelial damage along the line of apposition of the valve cusps and deposition of fibrin on the smooth surface of the valve and in the commissures (Magarey, 1951), but the nature of the ultimate deformity of the chordae tendineae may be influenced by the geometry of the scarred valve. Rusted *et al.* (1956) examined the pathology of mitral stenosis and placed valves into one of 3 general categories. The categories and relative incidence are (1) scarring of cusps or commissures or both (61%); (2) scarring of cusps or commissures, with shortening of the chordae tendineae (30%); and (3) chordal shortening alone (9%). Harken *et al.* (1951) classified mitral stenosis as type I, in which there is a rigid, scarred, and diaphragm-like valve with essentially normal chordae tendineae, or type II, in which the valve forms an elastic funnel with fusion of the chordae tendineae. Both Harken *et al.* (1951) and Rusted *et al.* (1956) found that the diaphragmatic type was more common than the funnel-shaped valve.

Angiographically, mitral stenosis may appear as a relatively immobile diaphragm-like structure at the ostium of the left ventricle with a slight reduction in the length of the chordae tendineae and chordae tendineae index, and enlarged papillary muscles with high papillary muscle hypertrophy index; or as a less discrete valve shadow with greater reduction in length of the chordae tendineae and chordae tendineae index, and slight enlargement of the papillary muscles with slightly increased papillary muscle hypertrophv index (Fig. 3 and 4). The Harken *et al.* (1951) classification into type I and type II closely corresponds to these two angiographic patterns.

The possibility that the length of chordae tendineae in mitral stenosis is influenced by the geometry and mobility of the valve is suggested by studies of valvar restenosis. Chordae tendineae and papillary muscle hypertrophy indices in patients with restenosis of the funnel-shaped subvalvar mitral stenosis are generally distributed above the mean for unoperated hearts (triangles in Fig. 3 and 4). This skewed distribution of data suggests that valvotomy increases the mobility of the valve and causes an elongation of the chordae tendineae and enlargement of the papillary muscle. By contrast, symmetrical distribution of chordae tendineae and papillary muscle hypertrophy indices in patients with restenosis of diaphragmatic valvar mitral stenosis about the mean for unoperated hearts suggests that movement and ventricular systolic forces exerted on the valve are essentially unchanged by valvotomy.

The finding that the chordae tendineae may lengthen and the papillary muscles enlarge after valvotomy for subvalvar mitral stenosis may have therapeutic implications. After viewing the thickened and shortened chordae tendineae of subvalvar mitral stenosis (type II, Fig. 2), the prospect of restoration of valve movement and elongation of the chordae tendineae after valvotomy might appear remote. The results of these ventriculographic studies may, however, provide additional incentives for reconstructive rather than replacement valve surgery for subvalvar mitral stenosis.

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References

Bittar, N., and Sosa, J. A. (1972). Functional anatomy of the stenotic mitral valve. *British Journal of Radiology*, **45**, 207–209.

Harken, D. E., Dexter, L., Ellis, L. B., Farrand, R. E., and Dickson, J. F. (1951). The surgery of mitral stenosis. III. Finger fracture valvuloplasty. *Annals of Surgery*, **134**, 722–742.

Lam, J. H. C., Ranganathan, N., Wigle, E. D., and Silver, M. D. (1970). Morphology of the human mitral valve. I. Chordae tendineae: a new classification. *Circulation*, **4**, 449–458.

Magarey, F. R. (1949). On the mode of formation of Lambl's excrescences and their relation to chronic thickening of the mitral valve. *Journal of Pathology and Bacteriology*, **61**, 203–208.

Magarey, F. R. (1951). Pathogenesis of mitral stenosis. *British Medical Journal*, **1**, 856–857.

Ross, R. S., and Criley, J. M. (1964). Cineangiocardiographic studies of the origin of cardiovascular physical signs. *Circulation*, **30**, 255–261.

Rusted, I. E., Scheifley, C. H., and Edwards, J. E. (1956). Studies of the mitral valve. II. Certain anatomic features of the mitral valve and associated structures in mitral stenosis. *Circulation*, **14**, 398–406.

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Functional status of patients with large ventricular septal defect and pulmonary vascular disease 6 to 16 years after surgical closure of their defect in childhood

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We have reviewed 27 patients now 6 to 16 years after closure of a ventricular septal defect at 3 to 12 years of age associated with pulmonary hypertension with a view to assessing their quality of life, respiratory function, and exercise performance.

All the patients led normal unrestricted lives. Their subjective lack of symptoms was, in general, confirmed by the results obtained from assessment of lung function tests and two-stage exercise testing in 19 volunteers. Abnormal ventilation in relation to work load was noted in 5 patients and a slightly low exercise cardiac output in 6.

Although the patients led normal lives and had a satisfactory response to exercise, measurement of pulmonary artery pressure showed striking pulmonary hypertension on effort.

Despite the satisfactory progress of these patients their more long-term future must be one of conjecture and their residual pulmonary hypertension, indicative of residual pulmonary obstruction, must lend weight to arguments for earlier closure of ventricular septal defect before 1 to 2 years of age when changes in the pulmonary vascular bed may be reversed after closure of the defect.

The first successful closures of ventricular septal defect were reported in 1955 (Lillehei *et al.*, 1955; Kirklin *et al.*, 1955) and so the early childhood survivors are now young adults. Without closure of their large ventricular septal defects many of these patients could have developed progressive pulmonary vascular obstruction leading to reversal of shunt and the Eisenmenger syndrome. The object of the present study is to evaluate the quality of life of long-term survivors of surgical closure of large ventricular septal defects with preoperative pulmonary hypertension and to assess their capacity for effort by formal exercise tests and resting and exercise haemodynamics. This study is essentially an extension of a previous clinical and haemodynamic study conducted 1 to 8 years after surgical correction (Hallidie-Smith *et al.*, 1969).

Patients

We were able to follow up 27 patients, 25 of whom had been included in the previous study (Hallidie-Smith *et al.*, 1969), now 6 to 16 years after operation. Before operation these 25 patients all had systolic pressures in the pulmonary artery at or within 15 mmHg of that in the systemic arteries; all had a pulmonary arteriolar resistance of 8 units or above but all had clinical, radiological, and haemodynamic evidence of a pulmonary blood flow in excess of systemic. The other 2 patients who were studied (cases 14 and 15—Table 1), 6 and 8 years after operation, respectively, had systolic pulmonary arterial pressures at systemic level but low pulmonary resistances and pulmonary/systemic flow ratios of 4:1 and 5:1, respectively.

Methods

Twenty-one patients were interviewed and examined and a further 6 patients were contacted by letter. Each patient available for examination was weighed and measured and the values expressed as expected centiles of normal (Tanner, 1958). Each was questioned about his or her symptomatology, occupation, and leisure activities.

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Table 1 *Clinical and haemodynamic data (19 patients)*

Case No.	*Sex*	*Age (y)*	*Age at operation (y)*	*Occupation*	*Physical recreations*	*Centile*		*Resting last recorded PAP (Systolic/diastolic) (mmHg)*	*Supine exercise (mmHg) (Systolic/diastolic mean)*				*Heart rate/min*	
									PAP		*BAP*			
						Ht	*Wt*		*Rest*	*Ex*	*Rest*	*Ex*	*Rest*	*Ex*
1	M	14	6	School	Numerous	50	75	65/45	80/35 45	115/65 80	145/75 90	150/85 110	80	106
2	M	16	8	Farmer	Football, cycling	10	15	60/25	90/40 65	160/55 100	140/70 100	180/90 110	90	154
3	M	26	10	Motor mechanic	Climbing	10	5	55/25	60/30 45	80/40 60	160/80 100	180/105 115	78	120
4	M	18	7	Farmer	Football, cricket, cycling	50	50	50/15	45/15 25	75/40 55	125/70 80	135/75 90	64	120
5	M	20	6	Chef	Cycling	3	3	40/18	45/15 25	85/25 35	130/80 100	155/80 100	85	110
6	M	22	8	Church organ builder	Cycling, football	25	25	50/20	60/35 50	115/55 75	120/80 95	130/90 110	72	130
7	M	24	10	Commercial traveller	Running, weight lifting	90	97	80/20	75/20 85	160/70 100	130/75 90	160/100 110	54	112
8	M	28	12	French horn player	Cricket, cycling	10	90	60/20	40/25 35	100/40 60	110/75 85	180/110 120	84	126
9	M	21	5	Clerical worker	Football	10	10	25/12						
10	M	23	10	Builders' labourer	Football	50	50	45/15						
11	M	24	8	Policeman	Numerous	97	97	30/15						
12	F	12	13	School	Numerous	97	75	45/15	75/30 40	115/40 60	125/75 90	130/85 100	72	124
13	F	14	6	School	Top class athlete and swimmer	50	25	45/15	80/40 60	110/60 80	130/80 95	140/90 110	90	120
14	F	14	8	School	Numerous	10	3	35/12	48/20 30	70/35 45	120/80 90	155/80 90	84	122
15	F	15	8	School	Numerous	3	10	40/12	45/15 30	70/25 40	145/80 105	155/80 120	84	108
16	F	16	5	School	Tennis	50	90	45/15	65/45 55	100/50 40	100/60 80	140/80 100	86	130
17	F	23	11	University student	Tennis, hockey	50	50	55/25	80/30 45	120/45 60	140/75 85	120/80 90	84	132
18	F	26	12	Factory worker	Dancing	3	50	35/12	40/15 25	70/25 35	140/65 75	150/75 90	74	118
19	F	16	4	School	Dancing, tennis	25	10	35/10						

PAP, pulmonary arterial pressure; BAP, brachial arterial pressure.

LUNG FUNCTION TESTS (19 patients)

Forced expiratory volume in one second (FEV_1) and vital capacity (VC) were measured on a dry spirometer. Total lung capacity (TLC) was measured using constant volume plethysomography (Dubois *et al.*, 1956). The carbon monoxide transfer factor (TLCO) was measured by the single breath method (Ogilvie *et al.*, 1957). A bronchodilator (isoprenaline 100 μg) was given to assess reversibility of airways obstruction if present.

EXERCISE TESTS

Nineteen patients volunteered for two-stage exercise tests. These were performed on a constant work-rate bicycle ergometer (Elema-Schönander) at a room temperature of 19 to 22°C. The stage I, or increasing work load, test was carried out with the patients performing upright bicycle ergometry starting at zero load and increasing by 100 kpm/minute. The test was stopped in 5 patients at 85 per cent of their predicted maximum heart rate (Astrand 1960) and continued until the patient could not continue in the other 14. Inspired ventilation was measured on a dry gas meter (Parkinson Cassu C.D.). Mixed expired concentrations of carbon dioxide (CO_2) and oxygen (O_2) were estimated (accuracy $\pm 0{\cdot}05\%$) on a URAS capnograph and Servomex OA 137 oxygen analyser. The analysers were calibrated with a range of previously determined CO_2/O_2 gas mixtures. These values were continuously monitored on a Mingograph 81 recorder and total ventilation (VE), oxygen intake (VO_2), and carbon dioxide output (VCO_2) were calculated. Throughout the test an electrocardiogram was simultaneously monitored on the recorder and oscilloscope screen from which the heart rate was measured. There was a period of 30 to 40 minutes' rest before the second stage.

The stage II, or steady state, exercise test was carried out in 18 patients at two-thirds of the previously determined maximum working capacity. Throughout exercise ventilation, electrocardiogram and expired O_2 and CO_2 were displayed on the Mingograph recorder as before. When steady state was reached—usually at about 4 minutes—the cardiac output was estimated using the indirect CO_2 Fick equation. Arterialised ear lobe blood was taken at rest and on exercise (after 4 to 5 minutes) for the determination of Pa_{CO_2}, Pa_{O_2}, and lactate (Hohorst, 1957). In 6 patients the blood samples were inadequate and corrected end-tidal CO_2 (Jones *et al.*, 1967) was used as an estimation of arterial CO_2. Mixed venous CO_2 ($P\bar{v}_{CO_2}$) was then determined by the plateau CO_2 rebreathing technique without correction for the downstream effect (Jones *et al.*, 1967). If the plateau was unsatisfactory an extrapolate of $P\bar{v}_{CO_2}$ was derived (Denison *et al.*, 1969).

CARDIAC CATHETERISATION

Fifteen patients agreed to have cardiac catheterisation performed with the object of measuring the pulmonary artery pressure at rest and during exercise in the supine position. The patients had already experienced at least one previous postoperative catheterisation so it was already known that 4 had a small residual ventricular septal defect. In 3 patients there was a significant step up in oxygen saturation and the ratio of pulmonary to systemic flow was 1·5:1 or less (cases 5, 6 and 8). The remaining defect could be detected only by green dye dilution technique (case 13).

Catheters were introduced percutaneously into a median cubital vein and brachial artery. The venous catheter was advanced to the pulmonary artery so that resting pulmonary arterial and brachial arterial pressures could be recorded and blood samples for oxygen saturation obtained. The zero level for the pressure measurements was the mid chest. The patients were then exercised supine for 3 minutes using alternate leg raising, the ankles being placed in wide slings with counterbalanced weights run over pulleys. The phasic pulmonary arterial and brachial arterial pressures were recorded throughout the exercise and the mean pressures each minute. Oxygen saturations were estimated at rest and immediately before the end of the exercise.

In 8 patients the arterial catheter was advanced into the left ventricle and after a 10-minute rest period the exercise test was repeated and left ventricular end-diastolic pressure recorded and left ventricular stroke work calculated at rest and after 3 minutes of exercise. Cardiac output was measured at rest and exercise by the indocyanine green dye dilution technique.

The day-to-day occupation of French horn playing of one patient (case 8) was simulated by blowing in the supine position with simultaneous recording of pulmonary arterial and brachial arterial pressures.

Six patients volunteered to exercise in the upright position on the bicycle ergometer with pulmonary and brachial arterial lines in position. They performed an increasing work load test, starting at zero load and increasing by 100 kpm each minute until their known maximum work load was reached. Measurements of pulmonary and brachial arterial pressures were made at rest, at minute intervals, and at maximum work load with the measurement made from the xiphisternum.

Results

Twenty-one patients were interviewed and examined and a further 6 patients were contacted by letter. All except 1 patient said that they were symptom free with normal exercise tolerance. The exception (case 16) was overweight but said she lacked energy and could not sustain a prolonged game of tennis. There were 14 male and 13 female patients. Ten were still attending school and one was a university student. Of the 15 who had left school, one (mentally retarded) is at a training centre, one young woman had married and had one healthy normal baby, and the others were all in full-time employment, 6 involving heavy manual work. Four of the male patients had married and had children. All the patients remarked that they felt completely unrestricted both at work and in their leisure time and the young men seemed to participate more than the average in active sports of many varieties. Before operation all the patients were under weight (many less than 3rd centile), and short in stature (many less than 10th centile). All improved after closure of the ventricular septal defect and 2 young men are above 90th centile for height (cases 7 and 11). The individual clinical and haemodynamic findings in 19 patients who volunteered for tests of lung function are detailed in Table 1.

LUNG FUNCTION TESTS (Table 2)

Lung function tests were normal for the group as a whole but 2 showed mild restrictive ventilatory defects (cases 2 and 12). The former patient also had a low total lung capacity, residual volume, and transfer factor. The latter had a normal transfer factor but total lung capacity was not measured. Two others (cases 10 and 16) had mild airways obstruction not reversed by bronchodilator and case 16 also had a reduced transfer factor. Neither gave a history of asthma and both were nonsmokers.

Table 2 *Lung function results*

Case No.	FEV_1 *(s)*	*VC*	$\frac{FEV_1 s}{VC}$ *(per cent)*	*TLC*	*TLCO*
1	2·40	3·00	80	4·25	21·8
2	2·45	2·80	88	3·60	21·7
3	3·85	4·05	95	—	—
4	3·80	4·90	78	6·85	32·5
5	2·80	3·50	80	5·60	35·6
6	4·20	5·35	79	6·10	35·9
7	4·50	5·40	83	—	—
8	3·10	3·70	85	5·30	26·9
9	3·70	4·20	88	6·30	28·7
10	3·10	4·50	69	6·10	33·1
11	4·60	5·20	88	6·81	35·2
12	1·85	2·25	82	—	17·2
13	2·10	2·50	84	3·30	18·2
14	—	—	—	—	14·7
15	2·60	2·80	93	4·10	14·3
16	2·05	3·05	67	3·90	19·2
17	3·10	3·90	79	5·00	20·6
18	2·00	2·20	91	3·90	18·0
19	2·30	2·40	96	3·40	20·1
Mean ± SD	3·00 ± 0·42	3·65 ± 0·47	84 ± 7	4·93 ± 0·74	24·4 ± 3·2
% Predicted mean ± SD	85·4 ± 14	90·2 ± 13		93·8 ± 15	86·9 ± 1·3
Norman range* % Predicted	80–120	80–120	> 75	80–120	> 75

FEV_{1S} forced expiratory volume in 1 second—litres/second; VC, vital capacity—litres; TLC, total lung capacity—litres; TLCO, carbon monoxide transfer factor—ml/mmHg per min.
*Normal data (Cotes, 1968).

INCREASING WORK LOAD TESTS (Table 3)

The increasing work load tests carried out on 11 male and 8 female patients showed a low maximum work load for the group as a whole. However, 5 patients were stopped when they reached 85 per cent of predicted maximum heart rate for normal subjects (Astrand, 1960). One male patient (case 2) stopped at 60 per cent of predicted maximum work load. The female patients were less enthusiastic than the males and averaged only 63 per cent of predicted maximum work load. Five stopped because of aching legs at a time when both heart rate and ventilation were quite appropriate for the work load reached. Two female patients (cases 13 and 16) had grossly abnormal ventilation for the work load reached and stopped because of breathlessness; case 16 was subsequently unable to complete the steady state exercise test. The results of these 2 female patients and 1 male patient (case 2) are the only definitely abnormal exercise responses.

STEADY STATE EXERCISE TEST (Table 4)

The cardiac and metabolic response to steady state exercise test was normal for the group. At rest blood gases and lactate were normal in all except case 13 who had a low Pa_{CO_2}. The cardiac output was calculated to be normal at rest in all patients but since the indirect Fick method can be variable at rest, these data are omitted.

The cardiac output during submaximal steady state exercise (Fig. 1) was within normal limits in 12 patients and below normal in 6 (cases 2, 5, 7, 9, 13, and 15). Three patients (cases 3, 8, and 13) had a high venous admixture ratio. Arterial oxygen tension was low in 5 (cases 3, 5, 7, 8, and 13) and blood lactate was marginally high in case 5.

Table 3 *Increasing work load test*

Case No.	*Sex*	*Maximum work load (W max) kpm/min*	$\frac{\textit{W max observed}}{\textit{expected}}$ *%*	*Heart rate at W max beats/min*	*Ventilation at W max l/min*
1	M	700	70	170	40·6
2	M	600	60	182	33·3
3	M	800	73	170	—
4*	M	1000	83	164	54·2
5	M	900	86	153	59·5
6*	M	800	67	175	56·8
7	M	1100	85	182	106·0
8	M	800	73	173	67·9
9*	M	900	82	186	58·7
10*	M	800	67	169	56·0
11*	M	1100	85	164	63·7
12	F	500	63	166	32·8
13	F	500	63	179	50·2
14	F	400	57	175	22·0
15	F	700	100	179	53·2
16	F	400	44	170	52·4
17	F	600	67	169	59·0
18	F	400	57	108	19·8
19	F	500	63	155	32·0
Mean ±		711	71	168	51
SD		23	13	17	20

*Exercise stopped at 85 per cent predicted maximum heart rate (Astrand, 1960). Predicted values from Godfrey *et al.* (1971b).

CARDIAC CATHETERISATION

The last known resting pulmonary arterial pressures before the present study are shown in Table 1, and the resting and exercise pulmonary and brachial arterial phasic and mean pressures and heart rates recorded during this study are also shown. Serial resting pulmonary arterial pressures of the 15 patients currently studied are shown in Fig. 2 and supine resting and exercise pulmonary artery pressure (after 3 minutes of alternate leg raising) are shown in Fig. 3 (15 patients).

Table 4 *Results of stage 2: steady state exercise test*

Case No.	*Oxygen intake (l/min)*	*Arterial PO_2 (mmHg)*	*Arterial Pa_{CO_2} (mmHg)*	*Lactate (mEq/l)*	*Cardiac output (l/min)*	*Venous admixture (Qs/Qt) (%)*	*Heart rate (beats/min)*	*Stroke volume (ml/min)*
1	1·08	92	35	2·6	8·0	2·4	143	53
2	1·26	86	37	2·7	7·7	2·7	152	51
3	1·44	68	32	3·2	10·5	7·2	180	58
4	1·57	88	40	1·1	10·7	2·4	123	87
5	1·69	75	29	6·0	8·8	4·1	152	57
6	1·46	87	34	2·7	11·0	3·4	142	78
7	2·05	75	28	—	12·3	5·0	170	72
8	1·41	72	31	3·8	11·8	6·8	141	84
9	1·48	100	36	2·0	8·7	0·5	155	56
10	1·37	95	41	—	10·3	1·9	149	69
11	1·60	103	39	1·5	13·5	0·3	129	104
12	0·92	105	39	1·9	7·1	—	135	53
13	1·15	56	30	5·1	6·7	11·3	165	41
14	0·71	—	42	—	5·8	—	169	34
15	1·06	102	32	4·3	6·9	1·0	138	50
17	1·31	99	27	2·7	9·6	2·0	139	69
18	0·77	103	37	1·5	7·0	0·2	91	80
19	0·99	98	35	2·0	7·4	1·4	134	55
Summarised data								
Mean ±SD	1·30 ±0·34	88 ±15	35 5	2·8 ±1·4	9·1 ±2·2	3·4 ±3·1	144 ±23	64 ±12
Per cent of predicted normal value								
Mean ±SD	—	—	—	—	80 ±11	—	95 ±16	85 ±18
Normal range	—	>85	—	2·0–5·5	80–120	1·0–4·4	80–120	80–120

Normal values taken from Spiro (1975). Qs/Qt, volume of right to left shunts as percentage of systemic cardiac output.

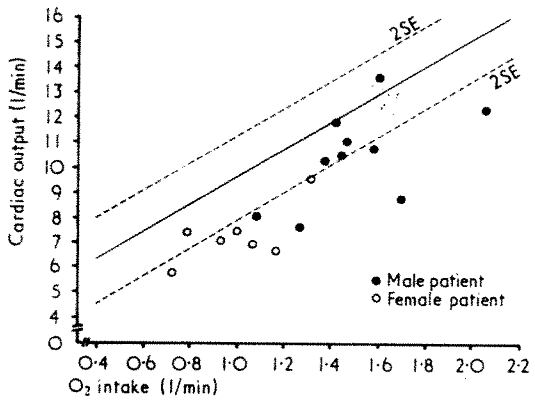

Fig. 1 *Cardiac output during steady state exercise related to oxygen consumption. Normal value lines from Godfrey* et al. *(1971a).*

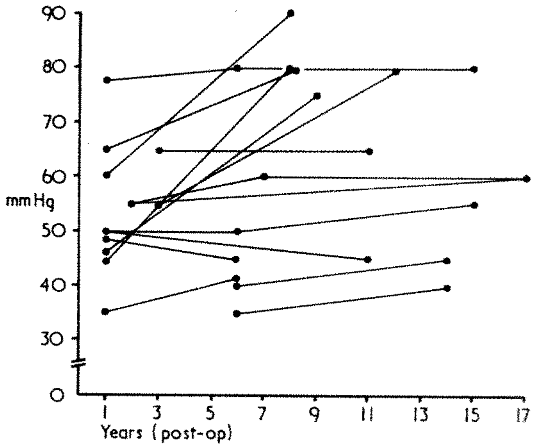

Fig. 2 *Serial resting systolic pulmonary arterial pressures (15 patients).*

Resting pulmonary arterial pressure (Fig. 4)
Of the 15 patients under discussion who volunteered for supine exercise recording of their pulmonary arterial pressure none could be considered to have a normal pulmonary arterial pressure (systolic pressure of 30 mmHg or less at rest). Values of 70 mmHg or more (systolic) were recorded in 8 patients. The serial recordings of pulmonary arterial pressure suggested that pulmonary hypertension might be progressive in 4 patients and in no patient could it be regarded as becoming less severe.

Supine exercise
The supine measurements of pulmonary and brachial arterial pressures and heart rate at rest and on effort are set out in Table 1, and the pulmonary arterial systolic pressures are shown in Fig. 3. It should be emphasised that the exercise called for only brief effort; this was not standardised and some patients put in much greater physical work than others who had to be much encouraged. In 5 patients the exercise pulmonary arterial pressure rose to close approximation with systemic (cases 2, 6, 7, 12, 13, and 17) and in all except 3 patients (cases 3, 14, and 15) the rise of systolic pulmonary arterial pressure was 30 mmHg or more.

Upright exercise (Table 5 and Fig. 4)
The upright maximum work load test with pulmonary artery and brachial artery lines *in situ* was completed by all 6 volunteers whose maximum work load was already known. In 3 patients the pulmonary arterial systolic pressure was within 30 mmHg of the systemic arterial systolic pressure at maximum work load (cases 1, 6, and 12).

Left ventricular function (Fig. 5)
Left ventricular stroke work was calculated in the 8 patients in whom left ventricular pressures were recorded at rest and after 3 minutes leg exercise.

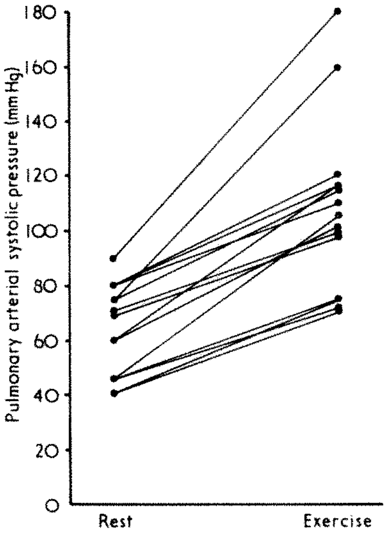

Fig. 3 *Pulmonary artery systolic pressure at rest and on completion of 3 minutes of supine leg raising (15 patients).*

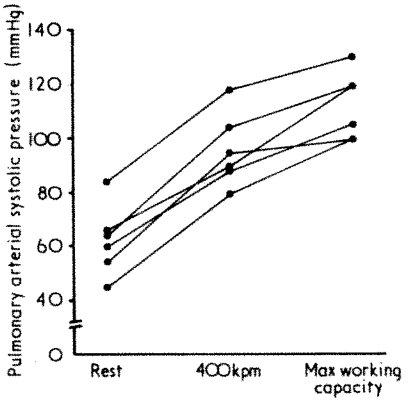

Fig. 4 *Increasing work load test pulmonary artery systolic pressure (6 patients).*

Table 5 *Bicycle progressive work load test in 6 patients*

Case No.	*Rest* *PA (mmHg)*	*BA (mmHg)*	*HR/min*	*At 400 kpm* *PA (mmHg)*	*BA (mmHg)*	*HR/min*	*Max work load* *PA (mmHg)*	*BA (mmHg)*	*HR/min*
1	84/45	158/100	84	118/60	148/100	130	130/75	150/110	190
3	55/32	102/60	90	95/55	100/80	135	100/60	150/85	180
5	45/15	130/80	92	80/30	160/90	142	100/40	160/105	196
6	66/35	105/60	70	90/45	120/80	115	120/80	130/85	194
8	60/25	120/80	88	88/40	130/80	122	105/45	155/100	196
12	65/30	134/84	98	105/70	140/90	160	120/80	145/90	180

PA, pulmonary arterial pressure; BA, brachial arterial pressure; HR, heart rate per minute.

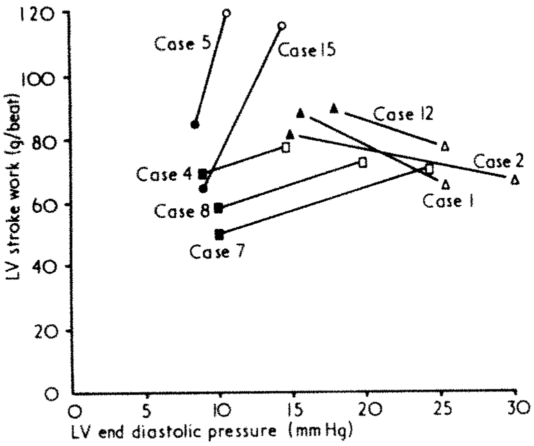

Fig. 5 *Left ventricular function at rest and during supine exercise in patients with repaired ventricular septal defect. Solid symbols: at rest; open symbols: during exercise.*

Left ventricular end-diastolic pressure was normal at rest in 5 of them and slightly raised in 3 (cases 1, 2, and 12), but on effort it rose to 20 to 30 mmHg in 5 of the 8 patients. Those patients with mild resting pulmonary hypertension were able to increase their left ventricular stroke work while maintaining a normal left ventricular filling pressure while those with more severe pulmonary hypertension had an abnormal rise in left ventricular filling pressure with either a small increase or fall in left ventricular stroke work, suggesting impaired left ventricular function.

Haemodynamics in simulated work

We were anxious to record haemodynamic events during the day-to-day life of our patients. One of them (case 8), a professional French horn player, volunteered to simulate blowing his instrument while on the catheter table with pulmonary arterial and brachial arterial pressures recorded simultaneously. We recorded a pulmonary arterial pressure varying between 70/20 and 100/75 mmHg during this manoeuvre with simultaneous corresponding brachial arterial pressure of 120/80 and 160/105 mmHg, respectively.

Discussion

There are few reports of the effects of a ventricular septal defect or pulmonary hypertension on lung function. Kimball and McIlroy (1966) described restrictive ventilation defects with high residual volumes in 3 patients with ventricular septal defects. McIlroy and Apthorp (1958) considered the effects of isolated pulmonary hypertension on lung function to be negligible, though a low carbon monoxide transfer factor possibly secondary to abnormal pulmonary vasculature has been occasionally described (Turino *et al.*, 1959).

In the present study 2 patients had restrictive ventilatory defects, 1 with a low transfer factor, possibly relating to pulmonary hypertension. Two other patients had mild irreversible airways obstruction which may have been the result of their previous recurrent chest infections in infancy. In the 4 patients with abnormalities of lung function the ventilation reached during exercise was below the calculated voluntary minute ventilation (as assessed by $FEV_1 \times 35$), suggesting that impaired lung function played no part in reducing maximum working capacity.

The majority of our patients have been shown to exercise normally but some have a low cardiac output on exercise which supports the findings of Maron *et al.* (1973) and Lueker *et al.* (1969), who exercised patients after closure of a ventricular septal defect in the upright and supine positions, respectively. Johnson (1962) and Jonsson and Lee (1968) showed that patients who had had a pulmonary valvotomy for pulmonary valve stenosis may also have a low cardiac output on exercise. The latter suggested that the peripheral circulation might be adapted to extract and use oxygen to a greater degree than normally and that persistence of this adaptive mechanism after operation might result in a lesser rise in cardiac output than is normally expected on effort. However, impairment of left or right ventricular function, or both, cannot be excluded and it could also be suggested that abnormal pulmonary vascular activity might limit cardiac output (Lueker *et al.*, 1969). However, in our series the finding of a low cardiac output on effort was not confined to those with severe pulmonary hypertension. Impaired left ventricular function has also been suspected in patients after closure of ventricular septal defect by finding raised left atrial pressures on exercise (Hallidie-Smith *et al.*, 1969; Maron *et al.*, 1973). More recently, Graham (1974) noted a decreased left ventricular ejection fraction in a similar group of patients. A decrease in left ventricular end-diastolic volume was also noted before operation, raising the question as to whether left ventricular function is ever normal in a patient with a large ventricular septal defect. Graham suggests that the decrease in ejection fraction may become apparent after operation because of the decreased after-load after closure of the ventricular septal defect. Our own findings are limited and relate only to postoperative studies but suggest that there may be impairment of left ventricular function on effort, most obvious in those patients with the more severe residual pulmonary hypertension.

In support of our patients' lack of symptoms we have the objective evidence of their varied employments, their sporting activities, sometimes keenly competitive, of their normal respiratory function tests and the normal exercise performance of the majority. These findings contrast with the conspicuously abnormal measurements of pulmonary arterial pressure recorded in the majority of patients at rest and in all patients on effort including the 2 patients in whom pulmonary vascular disease was not detected before operation. Some of our patients must be subjected to severe pulmonary hypertension during the course of their day-to-day activities as shown by our French horn player (case 8) whose increase in pulmonary arterial pressure could not be explained on the basis of a raised intrathoracic pressure or normal Valsalva response (Lee *et al.*, 1954). Our overall findings of pulmonary hypertension suggest that preoperative changes in the pulmonary vascular bed have failed to resolve to a greater or lesser extent. Thus, even those patients with a normal or nearly normal resting pulmonary arterial pressure may show a pronounced increase in pulmonary arterial pressure on effort because of limitation of the pulmonary vascular bed, perhaps related to lack of elasticity of small pulmonary vessels or fixed pulmonary vasoconstriction.

Serial records of pulmonary arterial pressure in our patients now 6 to 16 years after closure of their ventricular septal defects have not suggested any remission of pulmonary hypertension though in 10 of the 15 patients there is no evidence of progression. However, in 5 patients there is some increase in pulmonary arterial pressure and Weidman and DuShane (1974) noted a progressive increase in pulmonary vascular resistance in 4 of 12 comparable patients.

It was recognised that all except 2 of our patients had developed pulmonary vascular disease before closure of their defect; but the 2 in whom it was not recognised (cases 14 and 15), nevertheless, had been shown to have exercise pulmonary hypertension, suggesting that they already had some reduction of their pulmonary vascular bed by obstructive disease before operation. Thus, it seems that pulmonary vascular disease may already be established by early childhood in any patient with a large ventricular septal defect. This may not completely regress after operation and indeed may progress. Vogel *et al.* (1974) have shown the importance of the vasoconstrictive element and it seems likely that those individuals whose pulmonary blood flow was appreciably increased by vasodilators when investigated before operation may have the best chance of good long-term results. However, the most important long-term prognostic factor may be the age at which the ventricular septal defect is closed. Our patients were all over 2 years of age at the time of closure of their defect but recent advances in surgical and cardiopulmonary bypass techniques have made closure of ventricular septal defects in infants over 6 months of age a safe procedure (Weidman and DuShane, 1974). The Eisenmenger syndrome is rare below the age of 2 years and it has been shown that pulmonary arterial intimal changes are rare in the first year of life (Hislop *et al.*, 1975), and in infancy failure of the pulmonary vascular resistance to fall may not necessarily imply a poor long-term prognosis (Wagenvoort and Wagenvoort, 1974). Thus it seems advisable to recommend closure of a large ventricular septal defect with pulmonary hypertension well before the age of 2 years to ensure a satisfactory long-term result and the results of the present series should act as impetus to early surgical correction. The life expectancy and prognosis of our patients must remain in doubt, perhaps on the continued ability of the right ventricle to sustain the severe pulmonary hypertension which has challenged it from birth, on adequate left ventricular function and on factors which determine the progressive nature of pulmonary vascular obliterative changes. Thus far, however, the quality of life for these young men and women has been very good and certainly superior to that expected of comparable patients with ventricular septal defects and pulmonary vascular disease treated medically.

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References

Astrand, I. (1960). Aerobic work capacity in men and women with special reference to age. *Acta Physiologice Scandinavica,* **49,** Suppl. 169.

Cotes, J. E. (1968). *Lung Function,* 2nd ed. Blackwell, Oxford.

Denison, D., Edwards, R. H. T., Jones, G., and Pope, H. (1969). Direct and rebreathing estimates of the O_2 and CO_2 pressures in mixed venous blood. *Respiration Physiology,* **7,** 326–334.

Dubois, A. B., Botelho, S. Y., Bedell, G. N., Marshall, R., and Comroe, J. H., Jr. (1956). A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *Journal of Clinical Investigation,* **35,** 322–326.

Godfrey, S., Davies, C. T. M., Wozniak, E., and Barnes, C. A. (1971a). Cardio-respiratory response to exercise in normal children. *Clinical Science,* **40,** 419–431.

Godfrey, S., Wozniak, E. R., Courtenay Evans, R. J., and Samuels, C. S. (1971b). Ear lobe samples for blood gas analysis at rest and during exercise. *British Journal of Diseases of the Chest,* **65,** 58–64.

Graham, T. P., Jr. (1974). Ventricular performance in patients following corrective surgery for congenital heart disease. *Advances in Cardiology,* **11,** 81–106.

Hallidie-Smith, K. A., Hollman, A., Cleland, W. P., Bentall, H. H., and Goodwin, J. F. (1969). Effects of surgical closure of ventricular septal defects upon pulmonary vascular disease. *British Heart Journal,* **31,** 246–260.

Hislop, A., Haworth, S. G., Shinebourne, E. A., and Reid, L. (1975). Quantitative structural analysis of pulmonary vessels in isolated ventricular septal defect in infancy. *British Heart Journal,* **37,** 1014–1021.

Hohorst, H. J. (1957). Enzymatische Bestimming Von L (+) Milchsäure. *Biochemische Zeitschrift,* **328,** 509–521.

Johnson, A. M. (1962). Impaired exercise response and other residua of pulmonary stenosis after valvotomy. *British Heart Journal,* **24,** 375–388.

Jones, N. L., Campbell, E. J. M., McHardy, G. J. A., Higgs, B. E., and Clode, M. (1967). The estimation of carbon dioxide pressure of mixed venous blood during exercise. *Clinical Science,* **32,** 311–327.

Jonsson, B. L., and Lee, S. J. K. (1968). Haemodynamic effects of exercise in isolated pulmonary stenosis before and after surgery. *British Heart Journal,* **30,** 60–66.

Kimball, K. G., and McIlroy, M. B. (1966). Pulmonary hypertension in patients with congenital heart disease pre- and post-operative hemodynamics, pulmonary function and criteria for surgical closure of defects. *American Journal of Medicine,* **41,** 883–897.

Kirklin, J. W., DuShane, J. W., Patrick, R. T., Donald, D. E., Hetzel, P. S., Harshbarger, H. G., and Wood, E. H. (1955). Intracardiac surgery with the aid of a mechanical pump oxygenator system (Gibbon type) report of eight cases. *Proceedings of the Staff Meetings of the Mayo Clinic,* **30,** 201–206.

Lee, G., Jr., Matthews, M. B., and Sharpey-Schafer, E. P. (1954). The effect of the Valsalva manoeuvre on the systemic and pulmonary arterial pressure in man. *British Heart Journal,* **16,** 311–316.

Lillehei, C. W., Cohen, M., Warden, H. E., and Varco, R. (1955). Direct vision intracardiac correction of congenital anomalies by controlled cross circulation; results in 32 patients with ventricular septal defects, tetralogy of Fallot and atrio-ventricularis communis defects. *Surgery,* **38,** 11–29.

Lueker, R. D., Vogel, J. H. K., and Blount, S. G. (1969). Cardiovascular abnormalities following surgery for left to right shunts. *Circulation,* **40,** 785–801.

McIlroy, M. B., and Apthorp, G. H. (1958). Pulmonary function in pulmonary hypertension. *British Heart Journal,* **20,** 397–402.

Maron, B. J., Redwood, D. R., Hirshfeld, J. W., Goldstein, R. E., Morrow, A. G., and Epstein, S. E. (1973). Post-operative assessment of patients with ventricular septal defect and pulmonary hypertension. Response to intense upright exercise. *Circulation,* **48,** 864–874.

Ogilvie, C. M., Forster, R. E., Blakemore, W. S., and Morton, J. W. (1957). A standardized breathholding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *Journal of Clinical Investigation,* **36,** 1–17.

Spiro, S. G. (1975). Cardiorespiratory adaptation at the start of exercise in normal subjects and patients with chronic obstructive airways bronchitis. *Acta Medica Scandinavica,* **176,** 301.

Tanner, J. M. (1958). Evaluation of physical growth and development. In *Modern Trends in Paediatrics,* p. 325. Ed. by A. Holzel and J. P. M. Tizard. Butterworth, London.

Turino, G. M., Brandfonbrenner, M., and Fishman, A. P. (1959). The effect of changes in ventilation and pulmonary blood flow on the diffusing capacity of the lung. *Journal of Clinical Investigation,* **38,** 1186–1201.

Vogel, J. H. K., Grover, R. F., Jamieson, G., and Blount, S. G. (1974). Long term physiologic observations in patients with ventricular septal defect and increased pulmonary vascular resistance. *Advances in Cardiology,* **11,** 198–122.

Wagenvoort, C. A., and Wagenvoort, N. (1974). Pathology of the Eisenmenger syndrome and primary pulmonary hypertension. *Advances in Cardiology,* **11,** 123–130.

Weidman, W. H., and DuShane, J. W. (1974). Course of pulmonary hypertension following surgical closure of ventricular septal defect. *Advances in Cardiology,* **11,** 131–134.

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Modified axial lead system in children[1]

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Preliminary studies have been made on the use of the modified axial lead system in infancy and childhood. A highly significant correlation between internipple distance and height suggested that internipple distance be used as an index for the selection of a template to facilitate placement of the chest electrodes (Z and X). A series of 4 triangular templates was designed. The use of a template one size too large or too small was shown not to lead to any significant error in waveform measurement. A further study showed that the reference level for the application of the praecordial electrodes should be the 5th intercostal space as for adults, but that no serious diagnostic error was likely to arise if the 4th or 6th intercostal space was chosen by mistake. A study of the Frank lead system suggested that the use of the 5th intercostal space as a reference level was more appropriate than the 4th intercostal space, which is generally adopted by users of that system. The conclusion reached was that the axial lead system is the preferred orthogonal lead system for children, with templates for 4 ranges of internipple distance (<10 cm; 10 to 15 cm; 15 to 20 cm; and >20 cm—adult build) being proposed to simplify electrode placement.

Three orthogonal lead electrocardiography is being used increasingly among adults but relatively little has been published on this subject in childhood. A few papers have described normal ranges in a limited number of children (Hugenholtz and Liebman, 1962; Namin and D'Cruz, 1964; Namin *et al.*, 1964; Liebman *et al.*, 1966; Ainger, 1967; Khoury and Fowler, 1967; Gamboa and White, 1968; Liebman *et al.*, 1971; Liebman *et al.*, 1973) but more extensive studies are needed. In our laboratories, a project has been established to define normal values for 3 orthogonal lead electrocardiographic measurements derived from the modified axial lead system (Macfarlane, 1969) applied to a large population of infants and children.

At the outset the need for a simple method to facilitate the positioning of chest electrodes in infancy and childhood was required. The originators of the axial lead system (McFee and Parungao, 1961) suggested that where the subject was a child, the standard distance (6 cm) adopted in the adult to separate the 3 anterior chest electrodes (Z–) from the central reference point of the equilateral triangle formed by them (Fig. 1) should be reduced in proportion to the height of the subject. Similarly the separation of the lateral X+ electrodes is height dependent.

Were this rule to be strictly applied to each subject the work involved would be complicated and would constitute a serious obstacle to the adoption of the system on a wide scale. An even greater difficulty could be expected to arise from the acknowledged difficulty of ensuring accurate measurements of height (or length) in the first two or three years of life when stable electrocardiographic recording requires the least possible disturbance to the subject. We decided, therefore, to seek a method for electrode application whereby a small number of triangular templates might be constructed, their size and application being determined by some simple measurement which accurately reflected linear growth in infancy and childhood. As part of the study, it was decided to check whether the use, in error, of a triangular template of a larger or smaller size than that required would substantially affect the recording.

McFee and Parungao (1961) indicated that the reference point with respect to which the praecordial electrodes should be centred in the adult was 2 cm from the left sternal edge in the 5th intercostal space; they considered this to be the centre of gravity of the heart. During much of infancy and childhood the heart is at a higher level in the thorax than in the adult, with the apex beat in the 4th left intercostal space so that its centre of gravity should also be above the 5th interspace. We decided to determine whether variation in the choice

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of reference level was clinically important in these age groups. The longitudinal reference was chosen to be 1 cm from the left sternal edge in infants and children.

Guller *et al.* (1974) have shown that displacement of the E electrode of the Frank (1956) system in infants causes considerable alteration in the vectorcardiographic loops derived from the 3 orthogonal lead electrocardiogram. This system has also been criticised for its particular sensitivity to any change in the interspace chosen for the application of the chest electrodes. Langner *et al.* (1958) proposed that the 4th intercostal space be used as the reference level for supine patients rather than the fifth, which Frank (1956) had suggested for subjects in an erect posture. It was decided, therefore, to make a limited study with the Frank system on the effect of interspace variation in infants and children.

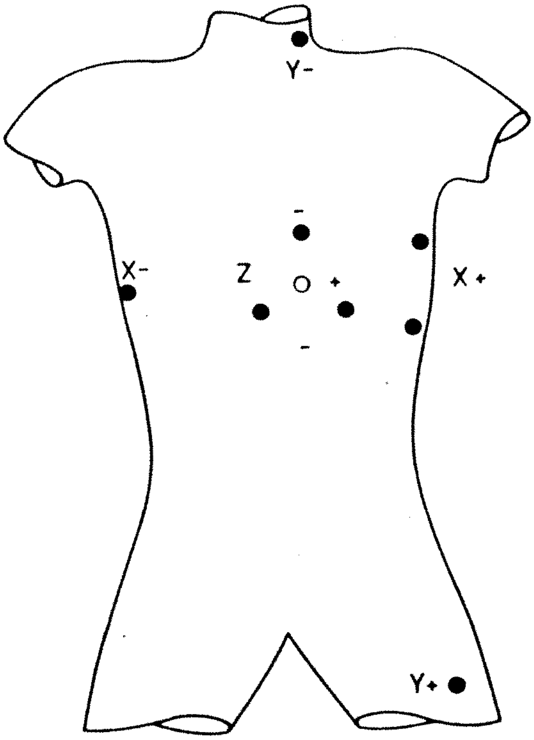

Fig. 1 *The electrode placements of the axial lead system. The reference point for the positioning of electrodes in adults was proposed as the 5th intercostal space, 2 cm to the left of the sternal margin. The X+ electrodes are placed symmetrically about the horizontal plane through this point with a separation of 11 cm in the adult, one-third of distance from the front to the back of the thorax. The X− electrode is placed at the reference level in a corresponding longitude on the right side of the chest. The Y+ electrode is usually placed on the left leg and the Y− electrode is positioned on the left side of the neck. The three anterior (Z−) electrodes are positioned at the apices of an equilateral triangle, each being 6 cm from the reference point (in the adult). This distance is also height dependent. The Z+ electrode is positioned on the back, at the reference level and directly behind the reference point.*

Subjects and methods

(a) SELECTION OF TEMPLATE SIZE

A total of 139 children between the ages of birth and 14 years (Table 1) was studied to determine whether or not there was any correlation between age, height, and certain other physical measurements which might serve as a guide to the selection of template size.

Measurements were made of trunk length (distance from vertebra prominens to tip of the sacrum), total body length, and the distance between the centre of each nipple. Infants were measured supine; older subjects were measured standing.

Subsequent to the choice of a series of triangular templates to facilitate the placement of the Z−electrodes, 24 subjects between the ages of 4 and 13 years were studied to determine the effect of using a template of incorrect size. In each case, the Z−electrodes were applied in accordance with the dimensions of (i) the correct triangle, (ii) the next larger triangle, and (iii) the next smaller triangle. The measurements derived from each recording for the purpose of comparisons were the maximum QRS vector magnitude (| QRS |), the angle in the transverse plane made by the projection of the maximum QRS vector (QRS $_T$), the amplitude of the R wave in the anterolateral lead X (R $_X$), the amplitude of the S wave in lead Z (S $_Z$), and the amplitude of the T wave in the anteroseptal lead (T $_Z$). For each of five parameters, comparisons were made between the measurements derived from recordings with the correct template size and those from the other two electrocardiograms, using the paired t test. It should be noted that, in practice,

Table 1 *Age distribution of 139 infants and children studied for correlation of age, height, etc.*

Age groups	*No. of subjects*
0– 6 d	24
1–51 w	31
1– 3 y	20
4– 6 y	37
7–10 y	13
11–13 y	14
	139

the polarity of lead Z was inverted so that an S_Z wave reflects movement of current towards the back.

(b) CHOICE OF INTERSPACE (AXIAL LEAD SYSTEM)

To explore the effect of changing the reference level for the chest electrodes, axial lead electrocardiograms were recorded with the 4th, 5th, and 6th intercostal spaces each as reference levels in 79 children and on the 4th and 5th interspaces in 29 infants, 18 of whom were neonates. In order to test the effect of variation of interspace with size of the child, these subjects were placed in four groups on the basis of internipple distance (Table 2).

The 295 electrocardiograms from these 108 children were analysed by a computer programme described previously (Macfarlane and Lawrie, 1974). The measurements selected for statistical purposes were $|QRS|$, QRS_T, R_X, S_Z, and T_Z as before. Comparisons of the measurements in records centred on adjacent interspaces were made using the paired t test.

(c) CHOICE OF INTERSPACE (FRANK SYSTEM)

A separate group of 61 children aged between 4 and 14 years was studied using the Frank lead system. The 3 orthogonal lead was recorded in the supine position twice, with the reference level taken on the first occasion as the 4th intercostal and on the second, as the 5th intercostal space. The 122 electrocardiograms obtained were analysed by the same programme as used for the axial lead data. This is allowable, since only QRS and T wave amplitudes were being considered with the diagnostic section of the programme being ignored. The wave recognition procedures used were thus the same for both the Frank and the axial lead systems.

Results

(a) SELECTION OF TRIANGULAR TEMPLATE SIZE FOR Z− ELECTRODES

Correlation coefficients relating height (length), age, and internipple distance are shown in Table 3, where the 139 children have been subdivided by age only (Table 1). Additional correlations were carried out for the 69 boys and 70 girls as two separate groups and these results are shown in Table 4. The correlations within each of the age groups were not as good as the overall correlation, as might have been expected. Trunk length correlated equally well with height (r=0·95 for girls and r=0·97 for boys) as did internipple distance.

On the basis of these results, internipple distance—being more easily measured than trunk length—was chosen as representative of height in prepubertal children. Four sizes of triangular template for the Z+ electrodes were designed to be used in conjunction with a table of internipple distance ranges (Table 5) representing the period from birth

Table 2 *Distribution of 108 children with respect to internipple distance to determine effect of varying reference level for electrode positioning*

Group	*Internipple distance (cm)*	*No. of subjects*
A	<8	18
B	8–8·9	11
C	9–12·9	24
D	>13	55
		108

Table 3 *Correlations between height, age, and internipple distance classified by age*

Age groups	*No. of subjects*	*Internipple distance v height*	*Age v height*	*Age v internipple distance*
0– 6 d	24	0·566	0·199	0·337
1–51 w	31	0·857	0·842	0·846
1– 3 y	20	0·463	0·744	0·327
4– 6 y	37	0·671	0·551	0·015
7–10 y	13	0·636	0·806	0·676
11–13 y	14	0·617	0·209	0·159
	139			

Table 4 *Correlations between measurements of height, age, and internipple distance, obtained from 69 boys and 70 girls*

Male ***Female***	*Internipple distance*	*Age*	*Height*
Internipple distance		0·87	0·95
Age	0·92		0·88
Height	0·96	0·96	

Table 5 *Template sizes for preliminary study, subdivided by internipple distance*

Group	*Internipple distance (cm)*	*Δ (cm)*	*X+ (cm)*
A	≤7·9	2	3·5
B	8–8·9	3	5·5
C	9–12·9	4	7
D	≥13	5	9

Δ, distance from centroid to apices of triangle formed by 3 Z− electrodes. X+, separation of X+ electrodes.

to puberty. The four groups were formed empirically from inspection of the scattergram of height v internipple distance (Fig. 2).

When measurements from electrodes applied in accordance with the correct triangle were compared with those arising from the use of a triangular template one size larger or smaller, no significant difference was discovered in 9 of the 10 measurements. However, slightly lower values for S_Z were obtained when a larger triangle than required was used. The probable explanation is that the triangle of larger size had the effect of positioning all three Z– electrodes further from the electrical centre of the heart, thus causing a decrease in the amplitude of the major deflection in the Z lead, i.e. the S wave.

(b) CHOICE OF INTERSPACE (AXIAL LEAD SYSTEM)

Correlation between measurements made at adjacent interspaces using the axial lead system on the four different subgroups of children separated with respect to internipple distance are summarised in Tables 6 and 7. Because numbers in the two groups with the smallest subjects were less than in the other groups, they were combined; this did not lead to any material difference in the results and the combined figures are not, therefore, presented. No significant difference between any of the values measured at the 4th and 5th intercostal spaces could be determined in the two groups containing the smallest subjects. In general, in these two groups, there was little difference between the mean amplitude and the different interspaces. With the one angular measurement (QRS_T) there was a large difference in the mean values but this was not statistically significant, because of the very large standard deviation.

In the remaining two groups of children correlations were made between measurements in the 4th and 5th, and in the 5th and 6th interspaces. In the group with internipple distances in the range 9 to

Table 6 *Correlations between electrocardiographic measurements recorded using modified axial lead system with reference level at 4th and 5th interspace*

	A	*B*	*C*	*D*
R_X	0·79	0·92	0·86*	0·85
S_Z	0·83	0·94	0·95	0·95
T_Z	0·31	0·72	0·57	0·87
| QRS |	0·90	0·96	0·90	0·92
QRS_T	0·32	0·75	0·99	0·99

Groups A, B, C, and D refer to internipple distance as indicated in Table 2.
*A statistically significant difference between measurements at different interspaces, even though correlation is high (P < 0·05).

Table 7 *Correlations between electrocardiographic measurements recorded using modified axial lead system with reference level at 5th and 6th interspaces*

	C	*D*
R_X	0·75	0·80
S_Z	0·94*	0·94
T_Z	0·91	0·85
| QRS |	0·85	0·89
QRS_T	0·99	0·98

Groups C and D refer to internipple distance indicated in Table 2.
*Statistically significant difference between measurements at different interspaces, even though correlation is high (P < 0·05).

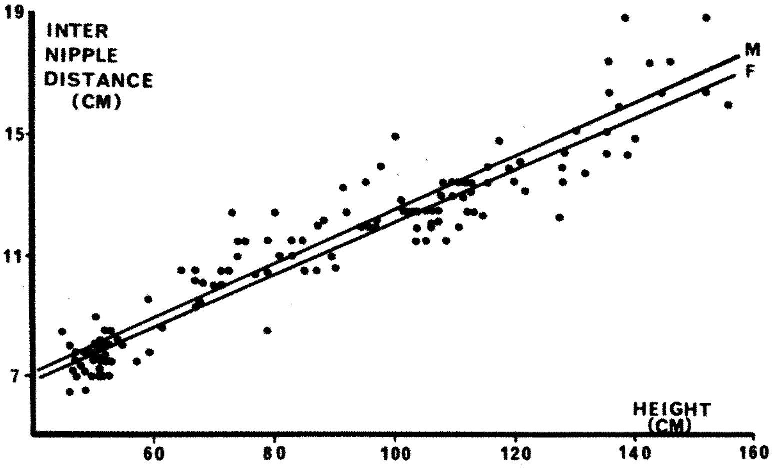

Fig. 2 *The scattergram of height and internipple distance formed from measurements on 70 girls and 69 boys aged from birth to 13 years. The regression lines for boys (M) and girls (F) are also shown. The equations are (a) for girls: internipple distance = 0·088 height + 3·3; (b) for boys: internipple distance = 0·092 height + 3·4.*

12·9 cm the R wave amplitude in the anterolateral lead (lead X) was significantly greater in the 5th than in the 4th interspace. No other comparison showed any significant difference between measurements at these two interspaces. Comparison of measurements between the 5th and 6th interspaces showed the only significant difference to be the amplitude of the S wave in the anteroseptal lead (lead Z) which was greater when recorded at the 5th interspace. With the fourth group of children with internipple distances of 13 cm or more there was no significant differences between any of the measurements compared.

(c) CHOICE OF INTERSPACE (FRANK SYSTEM) The 61 patients who had a Frank system orthogonal electrocardiogram were taken as a single group for the purpose of statistical analysis; this was valid since the paired t test was being used with each subject as his own control. In only one instance, viz. the maximum QRS spatial vector magnitude, was there any significant difference between measurements made using the 4th and 5th interspaces, the higher voltage being recorded from the 5th interspace.

Discussion

McFee and Parungao (1961) recommended that in childhood the spacing of the three anterior chest electrodes of the axial system should be adjusted in proportion to the height of the subject. It was considered to be impractical in routine electrocardiography to measure the height, especially of small children, before making a recording. Accurate measurement would be difficult to achieve without disturbing the child, thereby creating a situation which would be far from ideal for the recording of an adequate electrocardiogram. It was, therefore, necessary to find a simpler measurement which would reflect height and could act as a guide to the choice of a template for positioning the electrodes. Our data showed that, while there was good correlation between age and height beyond 1 year as might be expected, there was an even better correlation of height with internipple distance in both boys and girls in this largely prepubertal population. The simple measurement of internipple distance was, therefore, adopted as an index of height with respect to which the triangular electrode placings would be chosen.

The subdivision of subjects by internipple distance into four groups is somewhat arbitrary and the appearances in the scattergram (Fig. 2) could justify various groupings. The error in positioning the three anterior electrodes using a template rather than in strict proportion to the patient's height is minimal and of no consequence. It was found that the use of a triangle larger or smaller than required also produced little change in the electrocardiogram. It has already been shown by Duchosal (1966) that rotation of the three chest electrodes through 60° produces no appreciable difference in the anteroseptal lead wave form. Therefore any error of the order of a few millimetres in positioning the electrodes will be of no consequence.

Likewise the spacing of the two left lateral chest electrodes is determined by the choice of template; the upper and lower electrodes can be most conveniently sited on either side of the reference level by using the length of one side of the template as a measure of X+ electrode separation. Any inaccuracy in positioning arising from this method would be minimal and almost certainly less than the actual diameter of electrodes normally used for recording the orthogonal lead electrocardiogram.

For these reasons, at the completion of the study, it was decided to choose a subdivision of internipple distance that could be easily remembered by technicians. Measurements of 10 cm, 15 cm, and 20 cm were selected as dividing lines for selection of template size and templates of appropriate size were constructed (Fig. 3). Table 8 shows template sizes and their relation to average height and internipple distance.

In spite of the fact that in the child, by contrast with the adult, the 4th intercostal space must, on clinical grounds, be closer to the physical centre of gravity of the heart than is the 5th intercostal space, the electrocardiogram did not suggest that the electrical equivalent dipole was at the higher interspace. With the axial system no significant difference emerged between measurements centred on the 4th and 5th intercostal space reference levels, with the exception of R_X which favoured the 5th interspace in one of the four groups. No appreciable diagnostic error would be likely to arise

Table 8 *Recommended template sizes for use with modified axial lead system*

Internipple distance (cm)	Δ	*X+*	*Average height*
< 10	2	3·5	55
10→15	3	5·5	85
15→20	4·5	8	130
> 20	6	11	170

Δ, distance from centroid of Z− triangle of electrodes to each electrode.
X+, corresponding separation of 2 X+ electrodes. Approximate average heights of subjects in each group are noted.

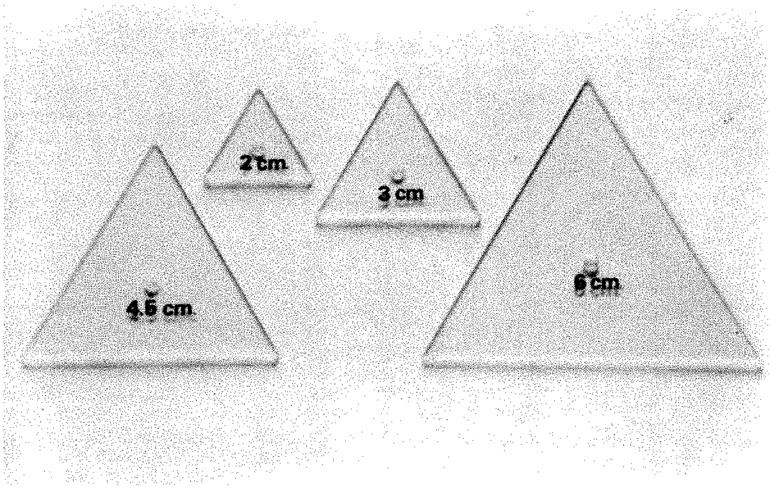

Fig. 3 *Perspex templates of four different sizes. The distances 2 cm, 3 cm, 4·5 cm, and 6 cm denote the distance from the centroid to the apices of each triangle and are recommended for children with internipple distances up to 10 cm, 15 cm, 20 cm, and over 20 cm, respectively. The latter applies to juveniles of adult build.*

if the 4th interspace were mistakenly selected instead of the 5th intercostal space. While there was no significant difference in angular measurements at different interspaces, the most dramatic change was observed in this value. This applied both to the axial system and the Frank system in the smallest subjects. No specific pattern to explain these differences was found. It is likely, however, that open vector loops in the transverse plane are responsible in that a shift of interspace may alter the pattern sufficiently to change the position of the maximum vector as illustrated in Fig. 4. The 5th intercostal space used in adults as the reference level for the thoracic electrodes in the axial system seems equally appropriate to some older children in the upper centile ranges for height and weight and approaching adult build. Moreover, with no evidence having been adduced from our studies to favour the selection for any age group of the 4th intercostal space, it is logical to propose that the 5th interspace should be used as the reference level for all children.

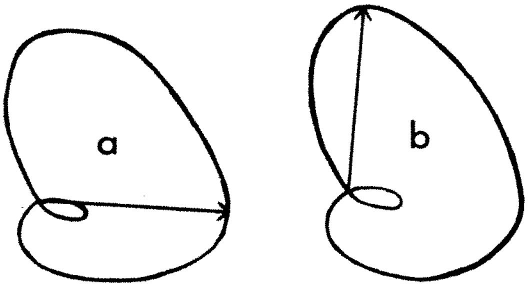

Fig. 4 *An illustration of how two similar vector loops, (a) and (b), may have maximum planar vectors separated by approximately 90°.*

Proponents of the axial system claim one of its advantages to be substantial freedom from error as a result of electrode misplacement. Some rotation of the praecordial electrode triangle has already been found not to lead to any significant change. We have now shown that a shift of the reference level from the 5th to the 4th or from the 5th to the 6th interspace does not cause changes of diagnostic significance. These findings strongly support the view that it is the axial nature of the lead field of this system rather than a meticulous placement of all the electrodes which ensures the orthogonality of the lead vectors and a stable electrocardiogram.

Guller *et al.* (1974), in their study of the Frank system in 50 children, have shown considerable changes in vector loops with displacement of only one of the anterior chest electrodes. Van Eck (1972) criticised the Frank system on theoretical grounds suggesting that the choice of the 4th interspace for use in children was questionable. In our study of the Frank system, the QRS vector magnitude was significantly higher in voltage ($P < 0{\cdot}05$) in the 5th intercostal space as compared with the 4th. These data suggest that the 5th interspace is the reference level of choice for the Frank system as it is for the axial lead system. This finding must cast some doubt on normal ranges previously published for the Frank system in children and confirm the suspicions of others as to the variability of this system in children. These studies support our view that the axial system is the orthogonal lead system of choice in children.

References

Ainger, L. (1967). Digital computer analysis of the vectorcardiogram of the newborn infant. *Circulation,* **36,** 906–923.

Duchosal, P. W. (1966). Practical remarks on the McFee and Parungao VCG lead system. *American Heart Journal,* **72,** 287–288.

Frank, E. (1956). An accurate, clinically practical system for spatial vectorcardiography. *Circulation,* **13,** 737–749.

Gamboa, R., and White, N. (1968). The corrected orthogonal electrocardiogram in normal children. McFee and Parungao lead system. *American Heart Journal,* **75,** 449–458.

Guller, B., Reeves, C., and Smith, R. E. (1974). Effect of E electrode position on Frank vectorcardiogram in children. *American Heart Journal,* **88,** 449–453.

Hugenholtz, P. G., and Liebman, J. (1962). The orthogonal vectorcardiogram in 100 normal children (Frank system) with some comparative data recorded by the cube system. *Circulation,* **26,** 891–901.

Khoury, G. H., and Fowler, R. S. (1967). Normal Frank vectorcardiogram in infancy and childhood. *British Heart Journal,* **29,** 563–570.

Langner, P. H., Okada, R. H., Moore, S. R., and Fies, H. (1958). Comparison of four orthogonal systems of vectorcardiography. *Circulation,* **17,** 46–54.

Liebman, J., Downs, T., and Priede, A. (1971). The Frank and McFee vectorcardiogram in normal children. A detailed quantitative analysis of 105 children between the ages of 2 and 19 years. In *Vectorcardiography,* Vol. 2, pp. 483–559. Ed. by I. Hoffman. North Holland, Amsterdam.

Liebman, J., Lee, M., Rao, P. S., and Mackay, W. (1973). Quantitation of the normal Frank and McFee-Parungao orthogonal electrocardiogram in the adolescent. *Circulation,* **48,** 735–752.

Liebman, J., Romberg, H. C., Downs, T., and Agusti, R. (1966). The Frank QRS vectorcardiogram in the premature infant. In *Vectorcardiography,* Vol. 1, pp. 256–271. Ed. by I. Hoffman and R. Taymor. North Holland, Amsterdam.

Macfarlane, P. W. (1969). A modified axial lead system for orthogonal lead electrocardiography. *Cardiovascular Research,* **3,** 510–515.

Macfarlane, P. W., and Lawrie, T. D. V. (1974). *An Introduction to Automated Electrocardiogram Interpretation.* Butterworths, London.

McFee, R., and Parungao, A. (1961). An orthogonal lead system for clinical electrocardiography. *American Heart Journal,* **62,** 93–100.

Namin, E. P., Arcilla, R. A., D'Cruz, I. A., and Gasul, B. (1964). Evolution of the Frank vectorcardiogram in normal infants. *American Journal of Cardiology,* **13,** 757–766.

Namin, E. P., and D'Cruz, I. A. (1964). Vectorcardiogram in normal children. *British Heart Journal,* **26,** 689–696.

Van Eck, H. J. R. (1972). The position of the X and Z lead electrodes in the Frank lead system—4th or 5th intercostal space. In *Proceedings of the XIIth International Colloquium Vectorcardiographicum,* pp. 606–609. Ed. by P. Rijlant. Presses Academiques Europeennes, Bruxelles.

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QRS voltage of the electrocardiogram and Frank vectorcardiogram in relation to ventricular volume

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Left ventricular volumes were estimated in 59 patients, who were investigated by single plane ventriculography and coronary arteriography. The relation of the left ventricular end-diastolic volumes to the QRS voltage of the 12-lead electrocardiograms and Frank vectorcardiograms was examined. It was found that the maximum spatial QRS voltage and the R wave voltage of leads V5 and V6 in patients without left ventricular hypertrophy were inversely correlated with end-diastolic volume.

This inverse relation of QRS voltage and left ventricular volume may explain loss of QRS voltage with dilatation of the heart. In patients with left ventricular hypertrophy QRS voltage is usually positively correlated with the degree of hypertrophy, but there is no significant correlation in the presence of cardiac dilatation. If the results of this study are extrapolated to patients with left ventricular hypertrophy an cardiac dilatation, then the inverse correlation of volume and QRS voltage may reduce the diagnostic sensitivity of unipolar chest lead and vectorcardiographic criteria of left ventricular hypertrophy.

Left ventricular wall thickness and mass have been correlated with QRS voltage of the 12-lead electrocardiogram and Frank vectorcardiogram; in life these measurements were made from the left ventriculogram (Hugenholtz *et al.*, 1968; Vine *et al.*, 1971) or by echocardiography (Bennett and Evans, 1974). QRS voltage has also been positively correlated with left ventricular end-diastolic volume (Baxley *et al.*, 1968; Vine *et al.*, 1971), but these studies have not distinguished the correlation with volume overloading of the left ventricle associated with left ventricular hypertrophy from any correlation of QRS voltage with volume alone.

The volume of the left ventricle is increased in many patients with left ventricular hypertrophy but the relation of QRS voltage to volume, in the absence of left ventricular hypertrophy, is unknown. This study explored these relations in patients without left ventricular hypertrophy and independently of variation of left ventricular mass.

Methods

Fifty-nine patients undergoing routine investigation for suspected coronary artery disease were included in the study. Thirty-six other patients examined were excluded from the study because of left ventricular aneurysm, other cardiovascular disease or intraventricular conduction defects. In all patients left ventriculograms and coronary arteriograms showed the wall and chamber of the left ventricle clearly when the heart rhythm was regular.

Routine 15-lead electrocardiograms, permitting derivation of the frontal and horizontal plane Frank vectorcardiograms, were performed on all patients. From these recordings the voltages of the R wave in leads X, Y, Z, aVL, V5, and V6 were measured. In addition the magnitude of the maximal spatial QRS voltage was computed from the simultaneous orthogonal vectors using the equation:

Spatial QRS voltage $= \sqrt{RX^2 + RY^2 + RZ^2}$ (Whitham, 1975) where RX, RY, RZ are the voltages of the QRS vector projected on the X, Y, and Z axes, respectively.

The QRS duration and the electrical axis of each 12-lead scalar electrocardiogram were also determined.

Left ventricular volumes were calculated by the area-length method (Kasser and Kennedy, 1969), using electronic planimetry by the same method as that of Sharma *et al.* (1976). Mean left ventricular wall thickness was derived from a planimetered area 4 cm in length along the anterior cardiac border at

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end-diastole; from the left ventricular wall thickness, and the total left ventricular volume at end-diastole, the left ventricular wall volume was calculated (Rackley *et al.*, 1964). The left ventricular mass was derived using 1·05 as the density of cardiac muscle (Bardeen, 1918).

The left ventricular volumes and QRS voltages were measured independently.

Results

Studies were made on 41 men and 18 women. The number of patients with normal left ventriculograms, the number with dyskinesia, and the number with left ventricular hypertrophy (left ventricular mass ⩾ 230 g—Kennedy *et al.*, 1966) are presented in Table 1. To describe the relation between QRS voltage and volume clearly, these patients have been divided into three groups: (1) Patients with normal coronary arteries who did not have left ventricular hypertrophy (21); (2) Patients with coronary artery disease who did not have left ventricular hypertrophy (27); (3) Patients with left ventricular hypertrophy whatever the anatomy of the coronary arteries and the function of the left ventricle (11).

Table 1 *The left ventricular wall*

	Normal coronary arteries			*Coronary artery disease*			*Total*
	Men	*Women*		*Men*	*Women*		
Normal thickness and function	10	9	21	7	1	27	27
Normal thickness with dyskinesia	1	1		14	5		21
Left ventricular hypertrophy	2	2		7	0		11
Total	13	12		28	6		59

The left ventricular volumes, left ventricular masses, wall thicknesses, and QRS voltages for the first group are shown in Table 2; similar measurements for the second group are presented in Table 3. The maximum spatial QRS voltage was inversely correlated with volume for group 1 (Fig. 1) and for group 2 (Fig. 2); both correlations were the same (r=0·68) and were significant at the 1 per cent level. There was no significant correlation for the group of patients with left ventricular hypertrophy.

The R wave voltages in leads V5 and V6 were also inversely correlated with left ventricular volume in groups 1 and 2, but these correlations were not significant in these small samples (group 1: =–0·46, P=0·03; group 2: r=–0·21, P=0·17). The voltage of the R wave in lead aVL, however, was positively, though also not significantly, correlated with volume in group 1 and group 2 (r=0·35, P=0·12, and r=0·24, P=0·10, respectively).

The maximum spatial QRS voltage was not significantly correlated with either left ventricular wall thickness or mass in patients without left ventricular hypertrophy but the numbers are small. There were also no significant correlations of left ventricular wall thickness, mass, or end-diastolic volume with any voltage measurement in patients with left ventricular hypertrophy (group 3).

Table 2 *QRS voltage, left ventricular volume and mass in patients with normal coronary arteries (group 1)*

Case No.	*Sex*	*R wave aVL (mV)*	*R wave V5 (mV)*	*Maximum spatial QRS voltage (mV)*	*Left ventricular volume (ml)*	*Left ventricular thickness (mm)*	*Left ventricular mass (g)*
1	F	0·6	1·8	1·9	112·8	7	127·8
2	F	0·3	1·5	1·8	150·5	11	224·3
3	M	1·1	1·6	1·2	168·0	9	181·7
4	M	1·1	1·8	1·5	120·5	8	131·3
5	F	0·1	1·4	1·6	83·6	7	107·3
6	M	0·0	1·3	1·4	198·4	8	176·1
7	F	0·1	2·0	2·2	103·4	9	132·4
8	F	0·9	1·3	1·6	116·7	6	89·6
9	M	0·2	1·3	2·1	122·3	9	143·1
10	M	0·7	2·3	1·3	140·7	9	169·1
11	M	0·1	1·7	1·9	98·7	8	117·8
12	M	0·3	1·2	0·9	175·7	8	184·6
13	F	1·1	0·6	1·0	179·0	9	186·7
14	M	0·7	1·5	1·3	193·0	11	224·5
15	F	0·2	1·8	2·0	99·5	10	168·1
16	M	0·4	1·0	1·0	155·9	8	149·8
17	F	0·9	1·6	2·2	123·1	7	113·0
18	M	0·3	2·4	1·7	117·6	8	94·2
19	F	0·8	1·2	1·3	151·0	10	142·0
20	F	0·2	1·3	1·5	120·6	7	112·4
21	M	0·8	0·9	1·9	131·9	8	129·5

A multiple regression equation was calculated from the data of groups 1 and 2 for the two independent variables, left ventricular wall thickness and left ventricular volume, and for the dependent variable, maximum spatial QRS voltage:

Maximum spatial QRS voltage (mV) $= 1{\cdot}34 + 0{\cdot}016\mathrm{th} - 0{\cdot}002\,\mathrm{vol}$, where th is the left ventricular wall thickness in mm and vol is the left ventricular volume in ml.

Discussion

This study has shown that in a selected group of patients without left ventricular hypertrophy, who

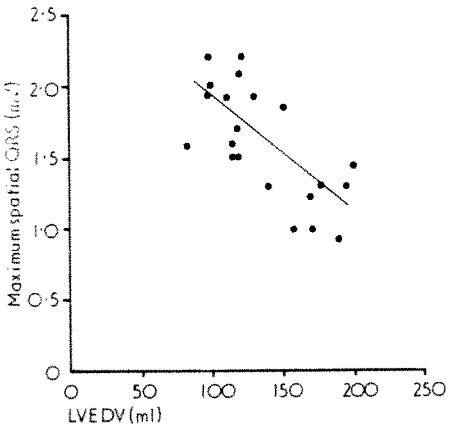

Fig. 1 *The maximum spatial QRS voltage in mV is plotted on the ordinate and the left ventricular end-diastolic volume (ml) is plotted on the abscissa for the patients with normal coronary arteries (group 1). The regression line is shown.*

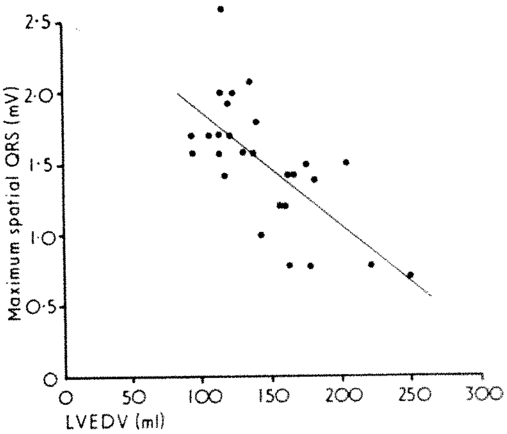

Fig. 2 *The maximum spatial QRS voltage in mV is plotted on the ordinate and the left ventricular end-diastolic volume (ml) is plotted on the abscissa for the patients with coronary artery disease (group 2). The regression line is shown.*

Table 3 *QRS voltage, left ventricular volume, and mass in patients with coronary artery disease (group 2)*

Case No.	*Sex*	*R wave aVL (mV)*	*R wave V5 (mV)*	*Maximum spatial QRS voltage (mV)*	*Left ventricular volume (ml)*	*Left ventricular thickness (mm)*	*Left ventricular mass (g)*
22	M	0·6	1·4	2·0	122·0	10	174·5
23	M	0·2	0·8	0·7	243·9	7	225·4
24	F	0·2	2·5	2·6	115·1	10	170·2
25	F	0·4	2·3	1·8	139·0	9	162·8
26	M	1·1	1·2	1·9	118·7	11	219·5
27	F	0·4	2·1	1·6	112·8	8	127·8
28	M	0·1	1·2	1·7	120·0	11	105·0
29	M	1·5	1·0	1·5	203·9	8	177·9
30	F	0·3	1·1	1·6	129·1	8	137·9
31	M	0·0	1·4	1·6	136·0	11	203·6
32	M	0·2	1·3	1·2	156·0	11	224·7
33	M	0·8	0·9	1·7	107·3	6	85·9
34	M	0·5	1·2	1·4	162·0	11	226·1
35	F	0·6	1·3	1·6	93·6	8	114·3
36	M	1·0	1·2	1·4	164·3	9	184·6
37	M	0·2	1·3	1·0	142·0	9	165·5
38	F	0·6	0·2	0·8	178·1	9	191·0
39	M	0·4	0·9	0·8	162·0	11	229·2
40	M	0·5	1·3	1·2	159·0	8	153·1
41	M	0·8	1·1	1·7	112·0	8	123·9
42	M	0·2	0·5	1·4	120·8	8	129·8
43	M	0·3	2·2	2·0	114·6	9	146·7
44	M	0·7	1·4	2·1	135·3	9	171·5
45	M	0·3	1·1	1·5	176·9	10	216·0
46	M	0·3	0·7	0·8	220·9	6	238·4
47	M	0·6	1·6	1·7	94·1	6	96·5
48	M	0·7	1·0	1·4	182·8	10	222·3

underwent coronary arteriography and left ventriculography for suspected coronary artery disease, the end-diastolic volume is inversely related to the maximum spatial QRS voltage of the Frank corrected vectorcardiogram. This was found whether the patients had coronary artery disease or not and was also found in the presence of dyskinesia despite the obvious departure of left ventricular shape from the ellipsoid formula. It was not found in a small group of patients with left ventricular hypertrophy, probably because of the opposite effect of hypertrophy on QRS voltage.

Day-to-day variation of the voltage of the electrocardiogram, vectorcardiogram, and the left ventricular volume are well known (Willems *et al.*, 1972). The calculation of left ventricular volume from single plane left ventriculograms has its limitations, being based on a hypothetical ellipsoid shape of the ventricle (Greene *et al.*, 1967), but measurements from biplane ventriculograms are only slightly more accurate (Dodge *et al.*, 1962; Baxley *et al.*, 1968; Kennedy *et al.*, 1970). However, errors introduced by these factors should tend to obscure any relation of QRS voltage to left ventricular volume and not accentuate it.

The electrocardiographic diagnosis of left ventricular hypertrophy is based on QRS voltage measurements and repolarisation changes of both the 12-lead electrocardiogram (Sokolow and Lyon, 1949) and the Frank vectorcardiogram. It is generally accepted that all voltage criteria are of similar diagnostic value, but there is little evidence for this. It has been found that an R wave voltage in lead aVL or over 1·0 mV indicates left ventricular hypertrophy (Talbot *et al.*, 1976). However, this criterion is only specific in the presence of a normal electrical axis, and is not as sensitive as either the maximal spatial QRS voltage, or criteria based on R wave voltage in leads V5 and V6. With the development of cardiac dilatation there is a diminution of the voltage of the R wave in leads V5 and V6, and therefore voltage criteria based on these leads become less sensitive. In a recent study these results were confirmed and in addition it was found that the voltage of the R wave in lead aVL was preserved in patients with left ventricular hypertrophy and cardiac dilatation (Talbot, 1975).

Rotation of the electrical axis superiorly and posteriorly which occurs in association with cardiac dilatation may partly explain these results. However, the position of the heart and the electrical axis do not affect the maximum spatial QRS voltage and yet this measurement is only slightly more sensitive to left ventricular hypertrophy than the praecordial voltage criteria of Sokolow and Lyon (Talbot *et al.*, 1976). This present study suggests that cardiac dilatation also affects the maximum spatial QRS voltage and it confirms that the voltage of the R wave in lead aVL is not inversely correlated with left ventricular volume. Since the QRS voltage in leads V5 and V6 is closely related to the maximum spatial QRS voltage, reduction of R wave voltage in these leads is to be expected, though other mechanisms may also play a part.

The discrepancy between the voltage of the R wave in lead aVL and the other voltage measurements in this study has not been explained, but discrepancies in voltage criteria of left ventricular hypertrophy between patients are well known. This is a good justification for multiple electrocardiographic leads.

Hugenholtz *et al.* (1968) have suggested without proof that QRS voltage is inversely correlated to volume but the reason for this association is unknown.

Bayley and Berry (1963) have suggested that increased intracavitary conductivity resulting from increased blood volume will augment the QRS voltage by local effects on the dipoles in the cardiac muscle (the Brody effect as first described by Brody (1956)). In addition, the proximity of the enlarged heart to the anterior chest wall will tend to increase the potential field in those areas, and Bayley and Berry (1963) have suggested that the surface potential may increase directly with the radius of the ventricular sphere. If so, these effects do not increase the voltage of the R wave in leads V5 and V6 in man, because of other influences.

However, if one considers the effect of the volume of blood on the dipolar activation fronts existing in the left ventricle it is not surprising that a reduction in the external electrical field is related to an increase in volume. As the volume increases, the internal surface of the left ventricle increases thus allowing more units, whether single dipoles or activation fronts, to have the highly conductive blood as the adjacent medium on at least one side. This will increase internal current flow which will have the effect of short circuiting some of the electrical field and hence reducing the external field.

In complex situations other effects may be important, but experimentally the reduction in QRS voltage with dilatation suggests that either the increased blood volume reduces the voltage by a short-circuiting effect or that in the dilated heart fewer muscle units are electrically active. All these theories are tentative since the relation of QRS voltage to left ventricular mass does not prove that muscle mass is the primary determinant of QRS voltage or that the distribution of left ventricular muscle and wall thickness are unimportant. Many studies that have correlated QRS voltage with left ventricular volume and mass have been very selective, usually excluding patients with ischaemia (Vine *et al.*, 1971) and not differentiating eccentric from concentric hypertrophy. In all studies correlations have only been moderate and the relation of mass to QRS voltage has deteriorated when the lesions were complex. Though these effects have not been quantified, it is felt that mixed types of overload, conduction disturbances, combined ventricular enlargement, congestive heart failure, and associated pulmonary and ischaemic heart disease, affect the relation of QRS voltage to left ventricular hypertrophy (Whitham, 1975).

If the association of left ventricular volume and QRS voltage could be extrapolated to changes in individual patients it might explain loss of voltage with the onset of cardiac dilatation in the presence of pressure overload of the left ventricle and absence of voltage criteria of left ventricular hypertrophy in the presence of left ventricular hypertrophy resulting from volume overload. However, more sophisticated statistical analysis of larger numbers of patients with left ventricular hypertrophy and varying degrees of volume overload will be needed to confirm this view.

References

Bardeen, C. R. (1918). Determination of the size of the heart by means of the *x*-rays. *American Journal of Anatomy*, **23**, 423–487.

Baxley, W. A., Dodge, H. T., and Sandler, H. (1968). A quantitative angiocardiographic study of left ventricular hypertrophy and the electrocardiogram. *Circulation*, **37**, 509–517.

Bayley, R. H., and Berry, P. M. (1963). 'Body surface' potentials produced by the eccentric dipole in the heart wall of the non-homogenous volume conductor. *American Heart Journal*, **65**, 200–207.

Bennett, D. H., and Evans, D. W. (1974). Correlation of left ventricular mass determined by echocardiography with vectorcardiographic and electrocardiographic voltage measurements. *British Heart Journal*, **36**, 981–987.

Brody, D. A. (1956). Theoretical analysis of intracavitary blood mass influence on the heart-lead relationship. *Circulation Research*, **4**, 731–738.

Dodge, H. T., Hay, R. E., and Sandler, H. (1962). Angiocardiographic method for directly determining left ventricular stroke-volume in man. *Circulation Research*, **11**, 739–745.

Greene, D. G., Carlisle, R., Grant, C., and Bunnell, I. L. (1967). Estimation of left ventricular volume by one plane cineangiography. *Circulation*, **35**, 61–69.

Hugenholtz, P. G., Ellison, R. C., and Mietinen, O. S. (1968). Spatial voltages in the assessment of left ventricular hypertrophy (Frank system). *Journal of Electrocardiology*, **1**, 77–90.

Kasser, I. S., and Kennedy, J. W. (1969). Measurement of left ventricular volumes in man by single-plane cineangiocardiography. *Investigative Radiology*, **4**, 83–90.

Kennedy, J. W., Baxley, W. A., Figley, M. M., Dodge, H. T., and Blackmon, J. R. (1966). Quantitative angiocardiography. I. Normal left ventricle in man. *Circulation*, **34**, 272–278.

Kennedy, J. W., Trenholme, S. E., and Kasser, I. S. (1970). Left ventricular volume and mass from single plane cineangiocardiogram. A comparison of anteroposterior and right anterior oblique methods. *American Heart Journal*, **80**, 343–352.

Rackley, C. E., Dodge, H. T., Coble, Y. D., and Hay, R. E. (1964). Method for determining left ventricular mass in man. *Circulation*, **29**, 666–671.

Sharma, B., Goodwin, J. F., Raphael, M. J. Steiner, R. E., Rainbow, R. G., and Taylor, S. H. (1976). Left ventricular angiography on exercise. A new method of assessing left ventricular function in ischaemic heart disease. *British Heart Journal*, **38**, 59–70.

Sokolow, M., and Lyon, T. P. (1949). The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *American Heart Journal*, **37**, 161–186.

Talbot, S. (1975). Electrical axis and voltage criteria of left ventricular hypertrophy. *American Heart Journal*, **90**, 420–425.

Talbot, S., Dreifus, L. S., Watanabe, Y., Chiang, R., Morris, K., and Reich, M. (1976). Diagnostic criteria for computer-aided electrocardiographic 15 lead system. *British Heart Journal*, **38**, 1247–1261.

Vine, D. L., Finchum, R. N., Dodge, H. T., Bancroft, W. H., Jr., and Hurst, D. C. (1971). Comparison of the vectorcardiogram with the electrocardiogram in the prediction of left ventricular size. *Circulation*, **43**, 547–558.

Whitham, A. C. (1975). *A System of Vectorcardiographic Interpretation*. Year Book Medical Publishers, Chicago.

Willems, J. L., Poblete, P. F., and Pipberger, H. V. (1972). Day-to-day variation of the normal orthogonal electrocardiogram and vectorcardiogram. *Circulation*, **45**, 1057.

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Training and electrocardiographic abnormalities in the elderly

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Electrocardiograms (CM5 lead, where one lead is attached in the V5 position and one at the manubrium sterni, with the neutral lead on the back of the neck) have been recorded from 14 men and 25 women aged 60 to 75 years, at rest, during progressive bicycle ergometer exercise to 75 to 85 per cent maximum oxygen intake, and during the subsequent recovery phase. Earlier studies showing a high frequency of ischaemic electrocardiographic abnormalities in women are confirmed; it is suggested that this may reflect a high work load per unit mass of myocardium. Training induces an elevation of the ST segment at rest and during recovery, with a reduction in ST depression during work at a given heart rate, the exercise changes being related to the intensity and frequency of training selected by the subject. Possible explanations of the response to regular exercise include not only the development of the collateral circulation, but also a lessening of the hyperkalaemia of effort and a reduction in the work load per unit mass of myocardium secondary to hypertrophy or a change in the average dimensions of the heart.

The increased frequency of abnormal exercise electrocardiograms with ageing is well documented (Åstrand, 1965, 1969; Doan *et al.,* 1965; Blackburn, 1969; Kasser and Bruce, 1969; Profant *et al.,* 1972; Cumming *et al.,* 1972, 1973). In men, it is generally accepted that there is a statistical association between an altered waveform of the ST segment during exercise and myocardial ischaemia, patients with such an abnormality having an increased risk of a 'coronary' attack (Blomqvist, 1965; Blackburn, 1969; Bruce *et al.,* 1969; Kasser and Bruce, 1969; Andersen *et al.,* 1971). In elderly women (Table 1), there is the paradox of an equally high frequency of abnormal records despite a much lower risk of ischaemic heart disease than that seen in the men (Åstrand, 1965; Ostrander *et al.,* 1965; Blackburn, 1969; Profant *et al.,* 1972; Cumming *et al.,* 1973).

Evidence regarding the influence of regular physical activity upon the electrocardiographic changes is conflicting. Saltin and Grimby (1968) noted that in athletes who continued sport into middle-aged and elderly life, ST changes were as common as in the general population, but lower frequencies of abnormalities were observed in ex-athletes. Roskamm *et al.* (1964) and Pyorala *et al.* (1967) had similar findings, but Holmgren and Strandell (1959) reported a relatively high frequency of electrocardiographic abnormalities in ex-athletes. Kavanagh and Shephard (1976) recently examined a substantial series of Masters' class track athletes (age-specific track contests for competitors from the fifth decade (Masters class I), sixth decade (class II), seventh decade (class III), and eighth decade + (class IV); in this group, ST changes were somewhat less frequent than in the general population. Cross-sectional studies suggest benefit from moderate effort. Blackburn (1969) commented that the incidence of post-exercise ST depression was less in farmers than in relatively inactive rail clerks, while Salzman *et al.* (1969) found that 79 per cent of persons who showed an improvement in physical fitness after training also showed decreases in ST abnormalities during submaximal cycling, improvements being directly related to adherence to the exercise programme and resultant reductions in heart rate at a given load. Bruce *et al.* (1969) found a 10 per cent decrease of heart rate in submaximal work with a 40 per cent improvement of ST segmental voltages; on the other hand, ST depression was unchanged in symptom-limited maximal work. Several other authors (Mazzarella *et al.,* 1966; Kilbom *et al.,* 1969; Detry and Bruce, 1971; Costill *et al.,* 1974) observed lesser abnormalities at a given work load, but no change in responses at a fixed heart rate after

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Table 1 *Frequency of 'positive' exercise tests in elderly subjects*

Men % Positive	Author	Women % Positive	Author
37	Cumming *et al.* (1972)	36	Brown and Shephard (1967)
46	Doan *et al.* (1965)	50	Åstrand (1969)
35	Åstrand (1969)	100	Profant *et al.* (1972)
32	Riley *et al.* (1970)	33*	Cumming *et al.* (1973)
25	Kasser and Bruce (1969)	21	Riley *et al.* (1970)
17	Kavanagh and Shephard (1976)		

*Though the authors cite a frequency of 33 per cent, their figures appear to show 9 of 33 cases (27%) with ST depression.

training. This implies that any effect of physical activity was the result of a reduction in the total cardiac work load rather than an improvement in myocardial oxygen supply. Kilbom (1971) found an increase in ST segment elevation during work and rest when middle-aged women were trained. However, the two subjects with initial ST depression did not improve.

Kavanagh *et al.* (1973) carried out experiments on a group of middle-aged 'post-coronary' patients. With training, some reversal of ST depression was found not only at a given work load, but also at a given heart rate; the favourable response was shown largely by younger patients who were able to push themselves to an intensive level of physical activity. Accordingly, it was thought of interest to examine the ST responses of a much older group of men and women, relating changes to the intensity of training undertaken.

Subjects and methods

The subjects were 14 men and 25 women aged 60 to 75 years. Though volunteers for a preretirement exercise class, the majority were quite sedentary when first enrolled (average bicycle ergometer prediction of aerobic power 22·6 ml/kg per min for the men and 21·0 ml/kg per min for the women, average of direct measurements on the treadmill 29·7 and 26·0 ml/kg per min for men and women, respectively). Apart from 3 men and 2 women, all were non-smokers. The group had also undergone a medical screening which had eliminated some 21 per cent before exercise testing on the usual clinical indications of unsuitability for participation in the exercise training programme. Specific contraindications to enrolment included uncontrolled metabolic disease, a diastolic pressure of more than 100 mmHg, heart failure, orthopaedic disabilities, regular medication other than laxatives or sedatives, history of angina or intermittent claudication, and major abnormalities of the resting electrocardiogram.

All electrocardiograms were recorded with the subjects in a resting but non-basal state. Strenuous physical exertion was avoided on the day of examination, and no meals or cigarettes were consumed within 2 hours of testing. Exercise was performed in an air-conditioned laboratory with a temperature of 22 ± 2°C. The subjects wore shorts, and in the case of the women a light halter top. All individuals were familiar with the investigators, and had at least one familiarisation ride on the ergometer before the definitive tests.

The bicycle ergometer was a standard Von Döbeln/Monark design, pedalled at 50 r.p.m. A 12-minute progressive submaximum exercise procedure was followed, with 4 minutes at each stage. The initial loading was 40 to 50 per cent of the estimated maximum oxygen intake and subsequent loadings were adjusted to produce a final heart rate corresponding to 75 to 85 per cent of maximum oxygen intake. After exercise, the subjects remained seated at rest on the bicycle throughout the first 6 minutes of recovery.

During the exercise procedure, the electrocardiogram was recorded by CM5 leads, starting with an initial 6 minutes of rest on the bicycle, continuing through the final 10 seconds of each minute of exercise, and onto the sixth minute of recovery. A Simpliscriptor electrocardiograph (model EK 100, Litton Medical Products) was used throughout. This apparatus meets American Heart Association specifications for high and low frequency response characteristics. Paper speed was set at 25 mm/s, and the gain was adjusted so that 1 mm of galvanometer deflection was equal to a signal of 0·1 mV. ST voltages were determined by simple inspection on a representative series of complexes, values being averaged over a respiratory cycle. The isoelectric line was defined by joining consecutive PR intervals, and the ST displacement was recorded at the end of the ST segment, immediately before the T wave.[1]

Exercise electrocardiograms were again recorded after 7 and 14 weeks of endurance training. Subjects met for an hour of supervised physical activity 4 times per week. The emphasis was on fast walking and jogging. An initial target pulse rate of 120 to 130 per minute was set, with progression to values of 140 to 150 per minute as the physical condition of the individual permitted. Class members were rated for the vigour and frequency of their participation, so that over the course of the study 4 self-

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[1] This measurement site avoids many of the artefacts that can produce ST depression in healthy young normal subjects (Lepeschkin, 1969).

Table 2 *Initial data showing average deviations of ST segmental voltage (mean ±SD) during bicycle ergometer exercise*

Time of measurement (min)	*Sex*	*ST segmental voltage (mV)*	*f_h (beats/min)*	*Work load (Watts)*	*Significance of deviation from isoelectric potential*
Rest, 6	M	±0·04 ±0·04	88 ±14	—	<0·01
	F	+0·01 ±0·08	80 ±13	—	NS
Exercise, 4	M	+0·03 ±0·08	103 ±14	36 ±15	NS
	F	−0·02 ±0·08	101 ±13	22 ± 9	NS
8	M	−0·02 ±0·06	118 ±10	66 ±21	NS
	F	−0·05 ±0·10	118 ±16	40 ±16	<0·01
12	M	−0·02 ±0·09	140 ± 8	97 ±30	NS
	F	−0·04 ±0·09	135 ±10	59 ±16	<0·05
Recovery, 2	M	+0·04 ±0·13	110 ±12	—	NS
	F	−0·02 ±0·08	98 ±14	—	NS
6	M	+0·02 ±0·05	100 ±12	—	NS
	F	−0·01 ±0·08	89 ±12	—	NS

Note: Elderly subjects (M, 14; F, 25), 4 minutes per stage of progressive test carried to 75 to 85 per cent of maximum oxygen intake.

selected training groups emerged (high frequency, high intensity; low frequency, high intensity; high frequency, low intensity; and low frequency, low intensity).

Results

INITIAL STATUS

Under resting conditions (Table 2), the men tended to have a small elevation of the ST segment ($P < 0{\cdot}01$); in women the group average resting ST voltage did not differ significantly from zero, though 1 woman showed a substantial (>0·1 mV) depression.

During exercise, ST voltages became slightly negative in both men and women, the trend for the women being statistically significant at heart rates averaging 118 and 135 beats per min ($P < 0{\cdot}01$ and $< 0{\cdot}05$, respectively); however, the averaged data showed no further increase of ST segmental depression from the second to the final work load.

During recovery, there was a gradual return of the ST voltage towards the isoelectric potential, but this process was still incomplete 6 minutes after stopping exercise.

Subjects showing clinically noteworthy ST changes are listed in Table 3. Exercise showed 8 women and 3 men with ST depression greater than 0·1 mV. During recovery, 1 further man and 1 further woman developed abnormal records. On the other hand, the 3 men and 4 of the 8 women who showed ischaemia during exercise did not show this phenomenon during recovery. Perhaps because they were health-conscious volunteers, the majority (79% men, 92% women) of our subjects were non-smokers; nevertheless, the percentage of abnormal electrocardiograms (29% in the men, 36% in the women) is much as in previous surveys of sedentary elderly people. Blackburn (1969) and Profant *et al.* (1972) have also commented that the proportion of abnormalities is influenced but little by smoking habits.

RESPONSE TO TRAINING

The physiological response to training varied with the self-selected intensity and frequency of effort; gains of maximum oxygen intake for the high frequency, high intensity group were as much as 30 per cent of the initial maximum oxygen intake, whereas changes in the low frequency, low intensity group were small and statistically insignificant (Sidney and Shephard, 1976b).

Resting electrocardiogram

After 7 weeks of training, there was an insignificant slowing of heart rate (2·9 beats/min). The resting electrocardiogram now showed an elevation of the ST segment; considering the results for both sexes together, the average change was 0·03 mV ($P < 0{\cdot}005$). At 14 weeks, the slowing of the resting heart rate (5·4 beats/min) was statistically significant

Table 3 *Occurrence of ischaemic changes in ST segment of electrocardiogram (≥0·1 mV depression) during bicycle ergometer exercise ($M = 14$, $F = 25$). Intensity of effort was increased progressively to reach 75 to 85 per cent of $Vo_{2\ \mathrm{max}}$*

Occurrence of ischaemic change	M	F
Exercise only	3	3
Recovery only	1	1
Exercise and recovery	0	5*
Total (exercise and/or recovery)	4 (29%)	9* (36%)

*One woman showed an electrocardiogram which indicated ischaemia at rest and during exercise and recovery.

($P < 0\cdot005$). At this stage, there was a further small increase of ST segmental voltage (0·01 mV), but the change from 7 to 14 weeks was statistically insignificant. The extent of the positive deviation was apparently related to the extent of training undertaken; the high frequency, high intensity group showed an 0·06 mV elevation over 14 weeks ($P < 0\cdot05$), and the high frequency, low intensity group also had an increase of 0·05 mV that was nearly significant, but there was no change in the low frequency, high intensity and low frequency, low intensity groups.

Exercise electrocardiogram

After 14 weeks of conditioning, the men showed decrements in exercise heart rates averaging 14 to 15 beats/min at each of the test work intensities, with increments in ST segment voltages averaging 0·04 to 0·06 mV (Table 4). In the women, the pretraining, post-training differences averaged 3 to 8 beats/min for heart rate and 0·01 to 0·07 mV for ST voltage; changes were significant for the first work levels only.

As a second approach to determining whether exercise ST segmental voltages were altered with physical training, we calculated linear regression equations relating ST segmental voltage to exercise heart rate for each individual. The ST segmental voltage corresponding to a fixed heart rate of 120/min was then predicted from these equations. A paired t test analysis of the data indicated that the potential of the ST segment at the fixed heart rate changed from –0·03 mV to +0·01 mV ($N = 38$, $P < 0\cdot01$), with 7 weeks of training, and from –0·03 mV to +0·03 mV ($N = 31$, $P < 0\cdot025$), with 14 weeks of training. The increase in potential of the ST segment was equal for both sexes (0·03 to 0·04 mV in men and 0·04 to 0·05 in women), but the pretraining, post-training differences were significant only for women. Classifying subjects according to the intensity and frequency of training, changes in the ST segmental voltage were significant only for the high frequency, low intensity group.

Eleven subjects initially showed ST depression greater than 0·1 mV during submaximal exercise. After 14 weeks of training, 5 of the 11 (4 women, 1 man) had improved to the point where the depression was less than 0·1 mV at the selected test heart rates. A further two men who failed to resolve their abnormality with 14 weeks of training did so over an additional 35 to 40 weeks of participation in the exercise class. One further woman had a substantial lessening of ST depression, although her final tracing was still clinically abnormal. The three remaining women showed no evidence of improvement. In addition, 1 woman and 1 man from the low frequency, low intensity group showed ischaemia in the final tests that had not been observed at the initial examination.

Recovery electrocardiogram

Considering all subjects, the 2-minute post-exercise tracing showed an insignificant elevation of the ST segment (0·01 mV) after 7 weeks of training. An additional 7 weeks of exercise class membership elicited no further changes. The largest elevations were seen in the high frequency, high intensity group (average 0·05 mV), but even this change was statistically insignificant. At the 6th minute of recovery, there was a 0·04 mV ($P < 0\cdot025$) increase of ST voltage after 14 weeks of training. Changes were again largest for the high frequency, low intensity group (7 weeks, 0·06 mV, $P < 0\cdot025$, 14 weeks, 0·05 mV, $P < 0\cdot025$) and the high frequency, high intensity group (7 weeks, 0·05 mV nonsignificant; 14 weeks, 0·09 mV, $P < 0\cdot001$).

Of the 6 subjects who initially showed clinically noteworthy ST depression after the ergometer test, 4 lost this sign as training proceeded.

Discussion

ABNORMALITIES IN WOMEN

The present data support the view of several earlier authors that electrocardiographic abnormalities are at least as common in elderly women as in men of

Table 4 *Changes in exercise heart rate and ST segmental voltage with 7 and 14 weeks of training: values are mean differences ±SD*

	Work rate (Watts)	*Sex*	*Heart rate (beats/min)*		*ST segmental voltage (mV)*	
			7 weeks	*14 weeks*	*7 weeks*	*14 weeks*
Load 1	36	M	–9·6 ±2·9¶	–14·3 ±3·1**	0·02 ±0·02	0·06 ±0·02*
	22	F	–5·8 ±1·5**	–8·4 ±2·0**	0·04 ±0·02†	0·05 ±0·02
Load 2	22	M	–7·5 ±2·7†	–14·5 ±3·0**	0·05 ±0·02‡	0·06 ±0·03*
	40	F	–7·2 ±1·5**	–8·5 ±2·2¶	0·03 ±0·02	0·07 ±0·02¶
Load 3	97	M	–8·0 ±2·8†	–15·3 ±3·2**	0·00 ±0·02	0·04 ±0·02*
	59	F	–4·6 ±2·4	–2·7 ±5·8	0·03 ±0·01†	0·01 ±0·02

*$P < 0\cdot05$, †$P < 0\cdot025$, ‡$P < 0\cdot01$, §$P < 0\cdot025$, ¶$P < 0\cdot005$, **$P < 0\cdot001$.

the same age. Several hypotheses have been advanced to explain the phenomenon; in the present instance, a number of these possibilities can be rejected.

(a) It has been suggested that doctors tend to order electrocardiographic tests on women only if clinical symptoms of angina are present (Lepeschkin, 1969). Factors motivating subjects to volunteer for the present study were similar in men and women (Sidney and Shephard, 1976a), so it is unlikely that the proportion of abnormal electrocardiograms in the women was boosted by sample selection.

(b) Since women tend to have a more horizontal ST segment and a smaller T wave than men, it has been postulated that a given segmental depression is more obvious in female subjects (Lepeschkin, 1969). This could explain a high frequency of reported anomalies in 'eyeball' studies (Profant *et al.*, 1972), but can hardly account for the series of carefully measured records showing frequent ST segmental depressions in elderly women. In the present experiments, data were referred to an isoelectric line drawn between consecutive PR segments; a small T wave and a more horizontal ST segment could conceivably have displaced our measurement site a little further into the diastolic phase in the women, but this would have reduced rather than increased the proportion of reported abnormalities.

(c) There have been suggestions that sympathetic activity is greater in women than in men at a given level of exercise. However, any difference must be small, since the heart rate at a given percentage of maximal effort is only a little higher in female subjects (Åstrand and Ryhming, 1954). There seems no strong evidence that vasoregulatory asthenia, hyperventilation, postural effects, and related ST artefacts are more prevalent in women than in men.

(d) Women have a higher proportion of body fat than men. The frequency of abnormal ST segmental responses increases with obesity (Blackburn, 1969), though the impact of sex on this correlation does not seem to have been explored.

(e) It has been suggested that women may have as much atheroma as men, and may be as liable to ischaemia during exercise, yet rarely suffer fatal consequences of the disease (Dawber *et al.*, 1957; Åstrand, 1965; Kannel and Feinleib, 1972). This would accord with Anderson's hypothesis that heart attacks reflect a 'vulnerable myocardium' (Anderson, 1973); hormonal factors and perhaps secondary differences in tissue mineral reserves serve to protect the female myocardium against ischaemia. At the age of 65, hormonal advantages of the female are fast waning. The present authors know of no good studies of atheroma and scarring of the myocardium in apparently healthy women; nor, unfortunately, are there data on the vulnerability of the tissues. However, angiograms often fail to support electrocardiograms showing apparent ischaemia in women (Likoff *et al.*, 1966). A further possibility is that the female myocardium has a normal 'vulnerability', but constitutional and cultural factors keep women from the sudden increments in cardiac work load that could precipitate an 'electrical' death; an electrocardiographic test that requires elderly women to work to the same percentage of maximum effort as the men may be culturally unrealistic!

(f) The quadriceps is generally weaker in women than in men. Thus, it might be argued that attempts to perform the same relative work load with weaker muscles give rise to a greater tachycardia, a greater increase of systolic blood pressure, and a greater increase in cardiac work load. Kasser and Bruce (1969) suggest that if the heart of an elderly person is sufficiently loaded, ST segmental depression can arise in the absence of significant coronary disease. In the present experiments, the final blood pressure was only marginally higher in the women than in the men (194 versus 191 mmHg), while the final exercise heart rate was slightly lower for the women. Total cardiac work loads, therefore, cannot be blamed for the high proportion of ST abnormalities in the women.

(g) Perhaps the most intriguing possible explanation lies in weakness of the cardiac rather than the skeletal muscle. Women typically have smaller hearts than men, and the same absolute cardiac work load thus throws a greater relative strain on unit volume of cardiac tissue. It is most unlikely that the capillary supply per unit mass of muscle is greater in women; thus if a woman is taken to the same heart rate/pressure product as a man, the woman would inevitably be more liable to myocardial ischaemia. Such a deduction reinforces the conclusion of Cumming *et al.* (1973) that there is a need to revise criteria of abnormality for the female electrocardiogram.

IDENTIFICATION OF MYOCARDIAL ISCHAEMIA

The present data reinforce the point made by Cumming *et al.* (1972) in studies of male subjects, that it is desirable to study both exercise and recovery records if all cases with electrocardiographic manifestations of ischaemia are to be identified. The relative prognostic significance of changes during and after effort remains undecided. However, in view of the clinical success of simple submaximal recovery examinations such as the Master test, and the reports of emergencies developing shortly after exercise (Bruce *et al.*, 1968; Shephard and Kavanagh, 1975), recovery data should not be rejected.

RESPONSES TO ENDURANCE TRAINING

The training induced reduction in electrocardiographic abnormalities at a given heart rate and blood pressure is in accord with an earlier study of subjects who trained hard (Kavanagh *et al.*, 1973). Many postcoronary programmes use relatively homoeopathic doses of exercise, and their failure to reduce ischaemia at a given heart rate or pulse-pressure product may reflect an insufficient intensity of physical activity. It is less certain that intense training can develop the collateral circulation, as might be expected from work with experimental animals. An alternative hypothesis is that a strengthening of the cardiac muscle and a reduction of mean ventricular radius decreases the work load sustained by unit volume of cardiac tissue.

The situation would then be the antithesis of that in the elderly untrained woman; electrocardiographic evidence of ischaemia would be reduced, but there would not necessarily be any correction of the underlying atheroma. A further possibility is that the well-trained subject releases less intramuscular potassium at a given intensity of effort (Blomqvist, 1969); this, also, would reduce ST changes.

The increase of voltage in the ST segment under resting conditions is not pathological—indeed Sjöstrand (1950) has related the phenomenon to a slow heart rate, while Saltin and Grimby (1968) have commented that endurance athletes show quite distinct ST elevation. Kilbom (1971) has previously seen the development of positive ST segmental voltages in middle-aged women in response to training. The significance of the phenomenon is unknown, though account should probably be taken of the altered resting status in deciding what is a clinically significant ST depression during exercise.

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References

Andersen, K. L., Shephard, R. J., Denolin, H., Varnauskas, E., and Masironi, R. (1971). *Fundamentals of Exercise Testing*. World Health Organization, Geneva.

Anderson, T. W. (1973). The vulnerable myocardium. *Lancet*, **2**, 1084–1085.

Åstrand, I. (1965). Exercise electrocardiograms recorded twice with an 8-year interval in a group of 204 women and men 48–63 years old. *Acta Medica Scandinavica*, **178**, 27–39.

Åstrand, I. (1969). Electrocardiographic changes in relation to the type of exercise, the work load, age and sex. In *Measurement in Exercise Electrocardiography*, pp. 309–321. Ed. by H. Blackburn. Charles C. Thomas, Springfield, Illinois.

Åstrand, P. O., and Ryhming, I. (1954). A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during sub-maximal work. *Journal of Applied Physiology*, **7**, 218–221.

Blackburn, H. (1969) (Ed.). *Measurement in Exercise Electrocardiography*. Charles C. Thomas, Springfield, Illinois.

Blomqvist, G. (1965). The Frank lead exercise electrocardiogram. A quantitative study based on averaging technic and digital computer analysis. *Acta Medicia Scandinavica*, **178**, Suppl. 440.

Blomqvist, G. (1969). Variations of the electrocardiographic response to exercise under different experimental conditions; deconditioning, reconditioning, and high altitude. In *Measurement in Exercise Electrocardiography*, pp. 323–341. Ed. by H. Blackburn. Charles C. Thomas, Springfield, Illinois.

Brown, J. R., and Shephard, R. J. (1967). Some measurements of fitness in older female employees of a Toronto department store. *Canadian Medical Association Journal*, **97**, 1208–1213.

Bruce, R. A., Alexander, E. R., Li, Y. B., Chiang, B. N., Ting, N., and Hornsten, T. R. (1969). Electrocardiographic responses to maximal exercise in American and Chinese population samples. In *Measurement in Exercise Electrocardiography*, pp. 413–444. Ed. by H. Blackburn. Charles C. Thomas, Springfield, Illinois.

Bruce, R. A., Hornsten, T. R., and Blackmon, J. R. (1968). Myocardial infarction after normal responses to maximal exercise. *Circulation*, **38**, 552–558.

Costill, D. L., Branam, G. E., Moore, J. C., Sparks, K., and Turner, C. (1974). Effects of physical training in men with coronary heart disease. *Medicine and Science in Sports*, **6**, 95–100.

Cumming, G. R., Borysyk, L., and Dufresne, C. (1972). The maximal exercise ECG in asymptomatic men. *Canadian Medical Association Journal*, **106**, 649–653.

Cumming, G. R., Dufresne, C., Kich, L., and Samm, J. (1973). Exercise electrocardiogram patterns in normal women. *British Heart Journal*, **35**, 1055–1061.

Dawber, T. R., Moore, F. E., and Mann, G. V. (1957). Coronary heart disease in the Framingham study. *American Journal of Public Health*, **47**, Suppl. 4–23.

Detry, J-M., and Bruce, R. A. (1971). Effects of physical training on exertional ST segment depression in coronary heart disease. *Circulation*, **44**, 390–396.

Doan, A. E., Peterson, D. R., Blackmon, J. R., and Bruce, A. R. (1965). Myocardial ischemia after maximal exercise in healthy men. A method for detecting potential coronary heart disease? *American Heart Journal*, **69**, 11–21.

Holmgren, A., and Strandell, T. (1959). Relationship between heart volume, total hemoglobin, and physical working capacity in former athletes. *Acta Medica Scandinavica*, **163**, 149–160.

Kannel, W. B., and Feinleib, M. (1972). Natural history of angina pectoris in the Framingham study. *American Journal of Cardiology*, **29**, 154–163.

Kasser, I. S., and Bruce, R. A. (1969). Comparative effects of aging and coronary heart disease on submaximal and maximal exercise. *Circulation*, **39**, 759–774.

Kavanagh, T., and Shephard, R. J. (1976). Characteristics of the master Athlete. *Proceedings of the National Academy of Sciences of the United States of America*. In the press.

Kavanagh, T., Shephard, R. J., Doney, H., and Pandit, V. (1973). Intensive exercise in coronary rehabilitation. *Medicine and Science in Sports,* **5,** 34–39.

Kilbom, A. (1971). Physical training in women. *Scandinavian Journal of Clinical and Laboratory Investigation,* **28,** Suppl. 119, 1–34.

Kilbom, A., Hartley, L. H., Saltin, B., Bjure, J., Grimby, G., and Åstrand, I. (1969). Physical training in sedentary middle-aged and older men. I. Medical evaluation. *Scandinavian Journal of Clinical and Labaratory Investigation,* **24,** 315–322.

Lepeschkin, E. (1969). Physiological factors influencing the electrocardiographic response to exercise. In *Measurement in Exercise Electrocardiography,* pp. 363–387. Ed. by H. Blackburn. Charles C. Thomas, Springfield, Illinois.

Likoff, W., Segal, B. L., and Kasparian, H. (1966). Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *Circulation,* **34,** Suppl. 3, 157.

Mazzarella, J., Skinner, J. S., and Evans, T. (1966). Effects of interval training on the exercise electrocardiogram. *Circulation,* **34,** Suppl. 3, 165.

Ostrander, L. D., Brandt, R. L., Kjelsberg, M. O., and Epstein, F. H. (1965). Electrocardiographic findings among the adult population of a total natural community, Tecumseh, Michigan. *Circulation,* **31,** 888–898.

Profant, G. R., Early, R. G., Nilson, K. L., Kusumi, F., Hofer, V., and Bruce, R. A. (1972). Responses to maximal exercise in healthy middle-aged women. *Journal of Applied Physiology,* **33,** 595–599.

Pyorala, K., Karvonen, M. J., Taskinen, P., Takkunen, J., and Kyronseppa, H. (1967). Cardiovascular studies on former endurance athletes. In *Physical Activity and the Heart,* pp. 301–310. Ed. by M. J. Karvonen and A. J. Barry. Charles C. Thomas, Springfield, Illinois.

Riley, C. P., Oberman, A., Lampton, T. D., and Hurst, D. C. (1970). Submaximal exercise testing in a random sample of an elderly population. *Circulation,* **42,** 43–51.

Roskamm, H., Reindel, H., Weissleder, H., Kessler, G., and Aletter, K. (1964). Zur Frage der Spätschäden nach intensiven Hochleistungsport. *Medizinische Welt,* **2,** 2170–2180.

Saltin, B., and Grimby, G. (1968). Physiological analysis of middle-aged and old former athletes. Comparison with still active athletes of the same ages. *Circulation,* **38,** 1104–1115.

Salzman, S. H., Hellerstein, H. K., Radke, J. D., Maistelman, H. W., and Ricklin, R. (1969). Quantitative effects of physical conditioning on the exercise electrocardiogram of middle-aged subjects with arteriosclerotic heart disease. In *Measurement in Exercise Electrocardiography,* pp. 388–410. Ed. by H. Blackburn. Charles C. Thomas, Springfield, Illinois.

Shephard, R. J., and Kavanagh, T. (1975). Mild or intense exercise in coronary rehabilitation? In *Proceedings, 20th World Congress of Sports Medicine, Melbourne, Australia.*

Sidney, K. H., and Shephard, R. J. (1976a). Attitudes towards health and physical activity in the elderly. Effects of a training programme. *Medicine and Science in Sports,* **8,** 246–252.

Sidney, K. H., and Shephard, R. J. (1976b). Frequency and intensity of exercise as determinants of the response to training in elderly subjects. *Medicine and Science in Sports.* Submitted for publication.

Siegel, W., Blomqvist, G., and Mitchell, J., II. (1970). Effects of a quantitated physical training program on middle-aged sedentary men. *Circulation,* **41,** 19–29.

Sjöstrand, T. (1950). The relationship between the heart frequency and the ST level of the electrocardiogram. *Acta Medica Scandinavica,* **138,** 200–210.

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Ischaemic heart disease in the elderly

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Studies were made for evidence of heart disease on 501 people aged 65 and more living at home; 22·4 per cent had clinical and/or electrocardiographic evidence of ischaemic heart disease. The prevalence of ischaemic heart disease increased with age, and was slightly greater in men than women.

The frequency of ischaemic heart disease increased with increasing current cigarette consumption and with total cigarette consumption. There was no increase in relation to any of the following possible risk factors: systolic and diastolic blood pressure, blood glucose, serum cholesterol, skinfold thickness, percentage of ideal body weight.

The survival over a 5-year period of all subjects with ischaemic heart disease did not differ significantly from that of all subjects together, but the mortality of subjects with ischaemic heart disease and an abnormal electrocardiogram was 1·5 to 2 times that of subjects in whom ischaemic heart disease was diagnosed on the basis of angina pectoris or past cardiac infarction, the electrocardiogram being normal.

The majority of studies of ischaemic heart disease in old age have been concerned with the modes of presentation of acute cardiac infarction (Rodstein, 1956; Pathy, 1967), and the detailed and extensive reports on the 'risk factors' for the disease (see Kannel and Dawber, 1974; Joint Working Party, 1976; Reid *et al.*, 1976) barely consider these in relation to the elderly, even though ischaemic heart disease is the commonest single cause of death in old age (Caird and Kennedy, 1976). Of the many 'risk factors' identified with varying degrees of certainty, none, except possibly high blood pressure (Kannel, 1976), has been shown to carry with it an excess risk of ischaemic heart disease in old age (Elmfeldt *et al.*, 1976). Apart from studies of the survival of elderly patients admitted to hospital with acute cardiac infarction (Biörck *et al.*, 1958; Librach *et al.*, 1976), and of the excess mortality associated with a variety of electrocardiographic abnormalities (Caird *et al.*, 1974), there is little information on the natural history and prognosis of ischaemic heart disease manifest late in life.

The present study was undertaken to establish the prevalence of ischaemic heart disease in a random sample of the elderly population, to identify factors related to this prevalence, and to investigate the survival of old people with respect to the presence or absence of clinically diagnosable ischaemic heart disease. The study is part of a detailed clinical, laboratory, and nutritional survey of old people living at home.

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Methods

Two stratified random samples, totalling 501 subjects, were drawn from people aged 65 and over living at home, the first from the whole elderly population of the town of Kilsyth (Andrews *et al.*, 1971), the second from six general practices in north Glasgow, as described by McLennan *et al.* (1973). The findings in the two samples were virtually identical, and they have, therefore, been combined for the purposes of the present investigation.

A full medical history, supplemented where appropriate by reference to general practitioner and hospital records, and including details of current drug therapy, was taken from each participant. It also included standard questionnaires on angina pectoris (Rose and Blackburn, 1968) and smoking habits (Medical Research Council, 1966). Total cigarette consumption was estimated by multiplying the number of cigarettes smoked by the number of years for which each subject admitted to smoking cigarettes. Subjects who smoked both pipe and cigarette tobacco were included in respect of their cigarette consumption.

A clinical examination was carried out, and in all except 14 subjects (3%) a standard 13-lead electrocardiogram was recorded, the tracings being classified by two observers according to the Minnesota code (Rose and Blackburn, 1968; Kennedy and Caird, 1972). In all subjects except those whose condition necessitated examination at home rather than at a clinic a standard six-foot posteroanterior chest radiograph was taken, and height and weight recorded.

The percentage of the subject's ideal weight was calculated from the nomogram of Anderson (1948). The thickness of skinfolds over the right subscapular region and right triceps were recorded using Harpenden calipers, and the arithmetic sum in mm of the two measurements taken as 'skinfold thickness'. Blood was taken by venepuncture between 11.00 a.m. and 2.00 p.m. for measurement of glucose by Autoanalyser as 'true glucose' and cholesterol by the method of Annan and Isherwood (1969). Risk factors with continuous frequency distributions (i.e. systolic and diastolic blood pressure, blood glucose, serum cholesterol, skinfold thickness, and percentage of ideal weight) were analysed by dividing the subjects into tertiles of the frequency distributions, after exclusions as detailed in Table 1. Table 2 gives the inclusive ranges of the middle tertiles of these continuous distributions.

Subjects in the first (Kilsyth) sample were followed up for 5 years, and those in the second (Glasgow) sample for 3 years after their initial examination, and their survival status, and if dead their date of death, determined. Survival curves were constructed by life table methods (Merrell and Shulman, 1955).

Diagnostic criteria

Ischaemic heart disease was diagnosed on the basis of positive answers to the questions on angina pectoris (in the absence of evidence of significant aortic valve disease), and/or a documented history of cardiac infarction, and/or an electrocardiogram showing codable Q/QS items according to the Minnesota code. Table 3 shows the diagnostic criteria in the 112 subjects in whom ischaemic heart disease was diagnosed.

Hypertensive heart disease was diagnosed in the presence of an electrocardiogram showing 'probable left ventricular hypertrophy' (i.e. both voltage and ST-T changes; Kannel *et al.*, 1970; Kennedy and Caird, 1972; Campbell *et al.*, 1974) and either an arterial blood pressure of 180/110 mmHg or

Table 1 *Subjects excluded from individual analyses*

	Reason for exclusion	*Number*
Smoking	Not recorded	4
Blood pressure	Antihypertensive therapy	58
Blood glucose	Not recorded	27
	Known diabetes	11
	Thiazides	44
	Total	82
Serum cholesterol	Not recorded	51
Skinfold thickness	Not recorded	102
Per cent of ideal weight	Not recorded	54

Table 2 *Range of middle tertile of continuous variables*

Sex	*M*		*F*	
Age (y)	*65–74*	*75+*	*65–74*	*75+*
Systolic blood pressure (mmHg)	155–170	155–180	160–185	165–195
Diastolic blood pressure (mmHg)	85–100	85–100	89–105	95–105
Blood glucose (mmol/l)*	4·9–6·1	5·3–6·1	4·9–6·1	5·4–6·3
Serum cholesterol (mmol/l)*	5·9–6·9	5·6–6·6	6·9–8·2	6·5–7·9
Skinfold thickness (mm)	17–27	17–22	23–33	17–29
Per cent of ideal weight	97–115	94–104	101–119	101–118

**For conversion from SI units to traditional units:* glucose: 1 mmol/l ≃ 18 mg/100 ml; cholesterol: 1 mmol/l ≃ 38·6 mg/100 ml.

Table 3 *Diagnostic criteria for ischaemic heart disease*

Manifestation	*Electrocardiogram*	*M*	*F*	*M+F*
Angina*	No electrocardiogram	3	2	5
	Electrocardiogram normal	10	10	20
	Q/QS items†	5	2	7
	Other codable abnormality†	11	13	24
	Total	29	27	56
Cardiac infarction*	Electrocardiogram	3	4	7
	Q/QS items†	4	4	8
	Other codable abnormality†	2	6	8
	Total	9	14	23
No symptoms	Q/QS changes†	7	26	33
All	No electrocardiogram	3	2	5
	Electrocardiogram normal	13 (31%)	14 (22%)	27 (25%)
	Q/QS items†	16 (38%)	32 (49%)	46 (43%)
	Other codable abnormality†	13 (31%)	19 (29%)	32 (30%)
	Total	45	67	112

*From questionnaire.
†See text for definition.

more, or a lower blood pressure when antihypertensive drugs were being taken. Conventional criteria were used for the diagnosis of valvular heart disease (Bedford and Caird, 1960); pulmonary heart disease was diagnosed when the electrocardiogram showed right ventricular hypertrophy (Goodwin and Abdin, 1959) and there were symptoms and signs of severe chronic respiratory disease. 'Mixed' heart disease was considered present when criteria for more than one form of definite heart disease were met in an individual subject. 'Definite unclassifiable' heart disease was diagnosed when there was no doubt of cardiac abnormality (e.g. left bundle-branch block or atrial fibrillation) but the available evidence did not allow a convincing diagnostic classification. Heart disease was described as 'doubtful' when evidence of cardiac abnormality was not beyond doubt (e.g. T wave flattening, or a minor increase in cardiothoracic ratio on the chest radiograph).

Results

PREVALENCE OF HEART DISEASE

The prevalence of the various forms of heart disease diagnosed in the 501 subjects is shown in Table 4: 112 subjects (22·4%) had ischaemic heart disease, 11 of whom also fulfilled the criteria for hypertensive heart disease. Four men and 24 women had only hypertensive heart disease as defined. Three men and 19 women had valve disease; of these, 5 had mitral regurgitation of uncertain origin, 5 rheumatic mitral stenosis and regurgitation, 11 aortic stenosis with or without regurgitation, and 1 'isolated aortic regurgitation' (Bedford and Caird, 1960). Three men had pulmonary heart disease. Fifty-three subjects (11%) had 'definite unclassifiable' heart disease as defined, and 28 (6%) had 'doubtful' heart disease. In all, 43 per cent had definite heart disease, the proportion being slightly greater in men than in women, and increasing with age. Of those with definite heart disease as defined, 51 per cent had ischaemic heart disease.

Table 5 shows the prevalence of ischaemic heart disease by age and sex in greater detail. It was present more often in men (25%) than in women (21%), the male/female prevalence ratio being 1·1 between the ages of 65 and 74, and 1·2 over the age of 75. Ischaemic heart disease increased in frequency with age in both sexes.

RISK FACTORS FOR ISCHAEMIC HEART DISEASE

Of subjects who had never smoked, 17 per cent had ischaemic heart disease, as compared with 29 per cent of current cigarette smokers, 26 per cent of ex-cigarette smokers, and 23 per cent of current smokers of pipes or cigars (Table 6). The difference between current smokers and those who have never smoked is significant at the 2·5 per cent level. There is also a statistically significant trend in the prevalence of ischaemic heart disease in relation to total cigarette consumption (Table 7).

Fig. 1 to 3 show the prevalence of ischaemic heart

Table 4 *Prevalence of heart disease*

Age (y)	*65–74*		*75 +*		
Sex	*M*	*F*	*M*	*F*	*Total*
No. of subjects	102	167	79	153	501
Ischaemic	21	29	20	31	101 (20%)
Hypertensive	1	9	3	15	28 (6%)
Valvular	0	8	3	11	22 (4%)
Pulmonary	2	0	1	0	3 (0·6%)
Mixed ischaemic and hypertensive	1	3	3	4	11 (2%)μ
Unclassifiable	14	8	14	17	53 (11%)
Total definite heart disease	39 (38%)	57 (34%)	44 (56%)	78 (51%)	218 (43%)
Doubtful heart disease	10	4	1	13	28 (6%)
No heart disease	53 (52%)	106 (64%)	34 (43%)	62 (61%)	255 (51%)

Table 5 *Prevalence of ischaemic heart disease by age and sex*

Age (y)	*65–69*		*70–47*		*75–79*		*80–84*		*85 +*		*All subjects*
Sex	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M + F*
No. of subjects	58	85 (1)	44 (1)	82 (4)	47 (4)	80 (1)	21 (1)	46 (2)	11	27	501 (14)
No. with ischaemic heart disease	12	20 (1)	10	12 (1)	14 (3)	19	6	8	3	8	112 (5)
% with ischaemic heart disease	21	24	23	15	30	24	28	17	27	30	22

Numbers in brackets are subjects without an electrocardiogram.

Table 6 *Frequency of ischaemic heart disease and current smoking habits*

Sex		*M* *No.*	%	*F* *No.*	%	*M+F* *No.*	%
Never smoked		2/16	13	44/249	18	46/265	17
Current smokers:							
Cigarettes/day	1–14	10/46	22	12/24	50	22/70	31
	15+	9/31	29	4/20	20	13/51	26
	All	19/77	25	16/44	36	35/121	29*
Ex-cigarette smokers		9/39	23	6/19	32	15/58	26
Pipe smokers		9/39	23	—	—	9/39	23
Ex-pipe smokers		1/5		—	—	1/5	

*Significantly different from subjects who never smoked: $\chi^2 = 6{\cdot}12$, d.f. = 1, $P < 0{\cdot}025$.

Table 7 *Frequency of ischaemic heart disease and total cigarette consumption*

Sex		*M* *No.*	%	*F* *No.*	%	*M+F* *No.*	%
Non-smokers		2/16	13	44/249	18	46/265	17*
Total cigarette	< 200 000	5/36	14	12/34	36	17/70	24*
consumption	> 200 000	26/91	29	8/27	30	34/118	29*

*Trend significant: $\chi^2 = 7.80$, d.f. 2, $P < 0{\cdot}025$.

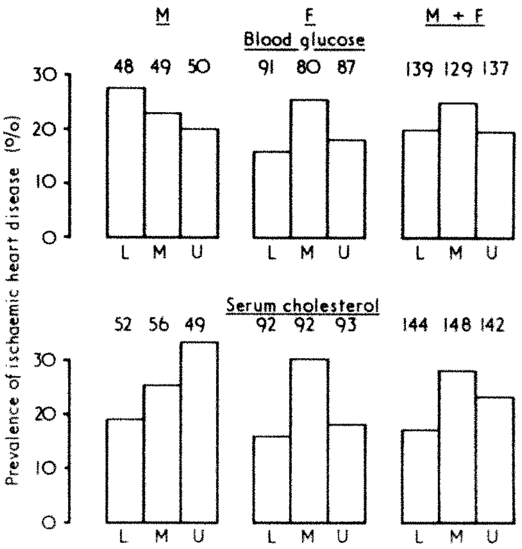

Fig. 2 *Prevalence of ischaemic heart disease by tertiles of the frequency distributions of blood glucose and serum cholesterol, in men, in women, and in both sexes together. There are no significant gradients of prevalence. L, M, U: lower, middle, and upper tertiles. Number of subjects in each group is shown above.*

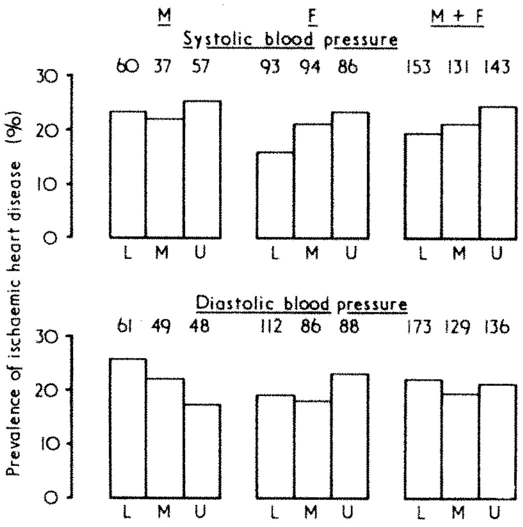

Fig. 1 *Prevalence of ischaemic heart disease by tertiles of the frequency distributions of systolic and diastolic blood pressure in men, in women, and in both sexes together. There are no significant gradients of prevalence. L, M, U: lower, middle, and upper tertiles. Number of subjects in each group is shown above.*

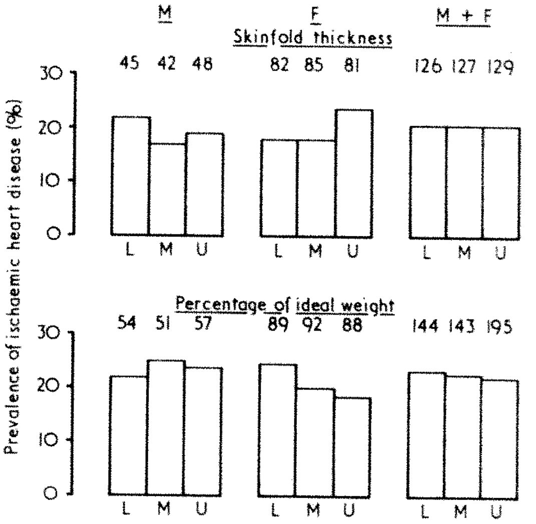

Fig. 3 *Prevalence of ischaemic heart disease by tertiles of the frequency distributions of skinfold thickness and percentage of ideal weight, in men, in women, and in both sexes together. There are no significant gradients of prevalence. L, M, U: lower, middle, and upper tertiles. Number of subjects in each group is shown above.*

disease by tertiles of the frequency distributions of systolic and diastolic blood pressure, blood glucose, serum cholesterol, skinfold thickness, and percentage of ideal weight. In none is there any significant gradient of prevalence. In the case of serum cholesterol, prevalence in women is highest in the middle tertile.

SURVIVAL IN ISCHAEMIC HEART DISEASE

The survival of the whole group of subjects with ischaemic heart disease does not differ significantly from that of an age- and sex-matched sample of the whole group of subjects (Table 8), but the survival of subjects whose electrocardiograms were abnormal (i.e. showed either Q/QS or other items) was significantly less than that of subjects with normal electrocardiograms in whom ischaemic heart disease was diagnosed solely on the basis of a history of angina or a past cardiac infarct.

Discussion

The reasons for regarding the population studied as representative at least of the elderly in urban Scotland, and probably more widely, are discussed by McLennan *et al.* (1973).

The diagnostic criteria for ischaemic heart disease used in the present study are probably as realistic as can be achieved in elderly people. It is known that questions relating to the presence of angina may be answered in the affirmative at one examination and in the negative at a second examination (Rose, 1968); the true prevalence of angina in any group is therefore likely to be underestimated in a single cross-sectional study. It will be seen from Table 3 that the electrocardiogram showed no codable abnormality in 40 per cent of the subjects who gave a history of angina. It is of course possible that the exertional chest pain recorded as angina by the answers to the questionnaire was not in fact of cardiac origin in some cases. But the electrocardiogram was normal in 7 of the 23 (30%) in whom the criterion for the diagnosis of ischaemic heart disease was a documented cardiac infarct. The findings of Kitchin *et al.* (1973) in the elderly are very similar. Of the 107 subjects in the present study in whom ischaemic heart disease was diagnosed and an electrocardiogram recorded, 43 per cent had Q/QS abnormalities, 30 per cent had other codable abnormalities, and 25 per cent had a normal electrocardiogram.

Table 8 *Survival of subjects with ischaemic heart disease*

		Survivors % (±SE) at years				
	No.	*1*	*2*	*3*	*4*	*5*
All cases	112	92 ±3	88 ±3	74 ±4	65 ± 5	56 ± 5
Expected*		93	86	78	71	65
Electrocardiogram normal	32	100	100	91 ±5	79 ± 8	79 ± 8
Q/QS items	46	89 ±5	87 ±5	67 ±7	67 ± 7	50 ±10
Other abnormality	29	86 ±6	72 ±8	61 ±9	48 ±10	37 ±10

*Expected mortality of all subjects, adjusted for age and sex.

It is possible that some instances of 'definite unclassifiable' heart disease were of ischaemic origin and should, therefore, be so classified, but it would be unwarranted and unrealistic to consider them all to be so. Certainly many cases both of bundle-branch block and of atrial fibrillation in old age are unrelated to coronary artery disease (Davies, 1976; Pomerance, 1976). The frequency of hypertensive heart disease depends largely on the definition of hypertension employed. The prevalences recorded in the present study for valvular and pulmonary heart disease are in line with previous estimates (Beford and Caird, 1960; Pomerance, 1976; Campbell *et al.*, 1974).

Male sex is a most important risk factor for ischaemic heart disease in the young and middle aged (Joint Working Party, 1976), but, as Table 5 shows, this is not so in the elderly, in whom the prevalence rate in men exceeds that in women by only 10 to 20 per cent (Kitchin *et al.*, 1973).

Analysis of other risk factors shows a significant association between ischaemic heart disease and cigarette smoking, which is demonstrable in both sexes and whether current or total cigarette consumption is considered (Tables 6 and 7). Kitchin *et al.* (1973), whose study of old people at home closely resembles the present investigation, failed to find such an association, but prospective data from the Framingham survey, reported by Kannel (1976), suggests that cigarette smoking retains its place as a risk factor for ischaemic heart disease in old age. Kannel also stresses the importance of high blood pressure as a risk factor for ischaemic heart disease in old age, but this is not confirmed either by Kitchin *et al.* (1973) or by the present study; both of these include many subjects over the age of 75 years. Neither blood glucose nor serum cholesterol level are associated with the presence of ischaemic heart disease (Fig. 2) as Kannel (1976) has also shown. In the case of serum cholesterol level, prevalence of ischaemic heart disease is highest in women in the middle tertile of the range, and it is of interest that Carlson and Böttiger (1972) in a prospective study found the highest incidence of episodes of ischaemic heart disease in elderly men whose serum cholesterol was in the middle of the frequency distribution.

Obesity is not of great importance as a risk factor for ischaemic heart disease in middle age (Epstein, 1973; Joint Working Party, 1976), and it is thus not surprising to find no association between either measure of obesity and ischaemic heart disease in old people (Fig. 3); indeed the gradient of prevalence is negative (i.e. ischaemic heart disease is commoner among the thinner subjects).

It seems clear, therefore, that cigarette smoking is the only one of the commonly demonstrable risk factors for ischaemic heart disease which can be positively identified in the elderly. Two possible explanations for the discrepancy between the findings in the middle-aged and in the elderly suggest themselves. It may be that those most exposed to risk factors in early and middle life do not survive into old age, or that all the risk factors continue to operate in old age, but each individually to a less than significant intensity, so that it is the duration of exposure to all factors together that comes to predominate. If this were so, it might well be that in old age no single risk factor could be shown to be significantly associated with the presence of ischaemic heart disease.

It is somewhat surprising that no excess mortality can be shown in old age for ischaemic heart disease when all subjects are taken together (Table 8). However, abnormality of the electrocardiogram, rather than the symptom of angina with a normal electrocardiogram, is shown to carry an excess mortality, as has been previously shown (Caird *et al.*, 1974). The difference in mortality between those with an abnormal electrocardiogram and that expected for the whole group of subjects is of the same order (1·5 to 2 fold) as was found by Biörck *et al.* (1958) and Librach *et al.* (1976) for elderly people discharged from hospital after a myocardial infarct, and is much less than for young or middle-aged patients with ischaemic heart disease.

This study shows clearly a substantial number of differences between ischaemic heart disease in middle and in later life. In old age the male predominance is very much smaller, the risk factors except cigarette smoking much less obvious, and the outlook for survival relative to other people of the same age much less unfavourable.

It is a pleasure to thank the general practitioners in Kilsyth and Glasgow for permission to study patients under their care; our colleagues in the survey, Drs. A. J. Akhtar, A. J. J. Gilmore, and W. J. McLennan, Miss A. Crombie, S.R.N., and Miss J. MacDougall, S.R.N., for their assistance; Dr. Gilmore and Dr. S. Acland for the follow-up data; and the subjects for their co-operation.

References

Anderson, A. B. (1948). Nomogram. Cited in *The Practice of Endocrinology*, p. 319. By R. Greene. Eyre and Spottiswoode, London. 1948.

Andrews, G. R., Cowan, N. R., and Anderson, W. F. (1971). The practice of geriatric medicine in the community. In *Problems and Progress in Medical Care: Essays on Current Research*, 5th Series, p. 58. Ed. by G. McLachlan. Oxford University Press, London.

Annan, W., and Isherwood, D. M. (1969). An automated method for the direct determination of total serum cholesterol. *Journal of Medical Laboratory Technology*, **26**, 202–211.

Bedford, P. D., and Caird, F. I. (1960). *Valvular Disease of the Heart in Old Age*. Churchill, London.

Biörck, G., Sievers, J., and Blomqvist, G. (1958). Studies on myocardial infarction in Malmö, 1935–1954. *Acta Medica Scandinavica*, **162**, 81–97.

Caird, F. I., Campbell, A., and Jackson, T. F. M. (1974). Significance of abnormalities of electrocardiogram in old people. *British Heart Journal*, **36**, 1012–1018.

Caird, F. I., and Kennedy, R. D. (1976). Epidemiology of heart disease in old age. In *Cardiology in Old Age*, p. 1. Ed. by F. I. Caird, J. L. C. Dall, and R. D. Kennedy. Plenum Press, New York and London.

Campbell, A., Caird, F. I., and Jackson, T. F. M. (1974). Prevalence of abnormalities of electrocardiogram in old people. *British Heart Journal*, **36**, 1005–1011.

Carlson, L. A., and Böttiger, L. E. (1972). Ischaemic heart disease in relation to fasting values of plasma triglycerides and cholesterol. *Lancet*, **1**, 865–868.

Davies, M. J. (1976). Pathology of the conduction system. In *Cardiology in Old Age*, p. 57. Ed. by F. I. Caird, J. L. C. Dall, and R. D. Kennedy. Plenum Press, New York and London.

Elmfeldt, D., Wilhelmsson, C., Vedin, A., Tibblin, G., and Wilhelmsen, L. (1976). Characteristics of representative male survivors of myocardial infarction compared with representative population samples. *Acta Medica Scandinavica*, **199**, 387–398.

Epstein, F. H. (1973). Coronary heart disease epidemiology revisited. *Circulation*, **48**, 185–194.

Goodwin, J. F., and Abdin, Z. H. (1959). The cardiogram of congenital and acquired right ventricular hypertrophy. *British Heart Journal*, **21**, 523–544.

Joint Working Party (1976). Prevention of coronary heart disease. *Journal of the Royal College of Physicians of London*, **10**, 213–275.

Kannel, W. B. (1976). Blood pressure and the development of cardiovascular disease in the aged. In *Cardiology in Old Age*, p. 143. Ed. by F. I. Caird, J. L. C. Dall, and R. D. Kennedy. Plenum Press, New York and London.

Kannel, W. B., and Dawber, T. R. (1974). Hypertension as an ingredient of a cardiovascular risk profile. *British Journal of Hospital Medicine*, **11**, 508–523.

Kannel, W. B., Gordon, T., Castelli, W. P., and Margolis, J. R. (1970). Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease. *Annals of Internal Medicine*, **72**, 813–822.

Kennedy, R. D., and Caird, F. I. (1972). The application of the Minnesota code to population studies of the electrocardiogram in the elderly. *Gerontologia Clinica*, **14**, 5–16.

Kitchin, A. H., Lowther, C. P., and Milne, J. S. (1973). Prevalence of clinical and electrocardiographic evidence of ischaemic heart disease in the older population. *British Heart Journal*, **35**, 946–953.

Librach, G., Schadel, M., Seltzer, M., Hart, A., and Yellin, N. (1976). Immediate and long-term prognosis of acute myocardial infarction in the aged. *Journal of Chronic Diseases*, **29**, 483–495.

McLennan, W. J., Andrews, G. R., Macleod, C., and Caird, F. I. (1973). Anaemia in the elderly. *Quarterly Journal of Medicine*, **n.s. 42**, 1–13.

Medical Research Council (1966). *Questionnaire on Respiratory Symptoms*. M.R.C., London.

Merrell, M., and Shulman, L. E. (1955). Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. *Journal of Chronic Diseases*, **1**, 12–32.

Pathy, M. S. (1967). Clinical presentation of myocardial infarction in the elderly. *British Heart Journal*, **29**, 190–199.

Pomerance, A. (1976). Pathology of the myocardium and valves. In *Cardiology in Old Age*, p. 11. Ed. by F. I. Caird, J. L. C. Dall, and R. D. Kennedy. Plenum Press, London and New York.

Reid, D. D., Hamilton, P. J. S., McCartney, P., and Rose, G. (1976). Smoking and other risk factors for coronary heart disease in British civil servants. *Lancet*, **2**, 979–984.

Rodstein, M. (1956). The characteristics of non-fatal myocardial infarction in the aged. *Archives of Internal Medicine*, **98**, 84–90.

Rose, G. A. (1968). Variability of angina—some implications for epidemiology *British Journal of Preventive and Social Medicine*, **22**, 12–15.

Rose, G. A., and Blackburn, H. (1968). *Cardiovascular Survey Methods. World Health Organization Monograph Series*, No. 56.

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Long-term prognosis of treated acute massive pulmonary embolism

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Seventy-two patients surviving initial treatment by pulmonary embolectomy, streptokinase, or heparin for acute massive pulmonary embolism have been reviewed 1 to 9 years later. Of these patients, 17 had additional cardiorespiratory disease. There were 12 late deaths (41% of those patients with, and 9% of those patients without additional cardiorespiratory disease). No death was due to chronic pulmonary hypertension, and none to certain recurrence of pulmonary embolism. The causes of death were malignant disease (6 patients), cardiopulmonary disease other than pulmonary embolism (4 patients), and 'sudden' (2 patients). Though venous interruption surgery was not used, and long-term anticoagulation rare, the incidence of possible or probable recurrent embolism was low (6%). There was no definite evidence of persistence or subsequent development of pulmonary hypertension after treatment in any patient. Resolution of embolism as judged by symptoms, signs, electrocardiogram, and chest x-ray *examination was almost always complete. Some pulmonary arteriograms 1 to 6 months after initial treatment showed minor abnormalities, but others at a later date were normal. Perfusion lung scans carried out 1 to 8 years after initial treatment often showed minor abnormalities.*

The fate of patients with acute massive pulmonary embolism may be sudden death, deterioration over a matter of hours or days resulting in death, or complete recovery taking a varying period of time. It has been suggested that some patients initially presenting with acute pulmonary embolism may develop chronic pulmonary hypertension (Magidson and Jacobson, 1955; Wood, 1956; Phear, 1960). Speculation exists whether chronic thromboembolic pulmonary hypertension represents the end-result of unresolved massive pulmonary embolism or the long-term accumulation of repeated unresolved minor emboli (Dalen and Alpert, 1975) in untreated patients.

During the period 1965 to 1973, 88 patients with acute massive pulmonary embolism were referred to the Brompton Hospital for treatment. Confirmation of the initial diagnosis was made in every case either by pulmonary arteriography or at pulmonary embolectomy. Many of these patients survived the initial episode of pulmonary embolism and form a group in which the long-term prognosis of pulmonary embolism can be assessed. This study was concerned with the causes of late death, the degree of resolution of pulmonary embolism, whether chronic pulmonary hypertension developed, and the incidence of recurrence of embolism.

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Definition of patients

During 1965 to 1973, 88 patients with acute massive pulmonary embolism were treated; of these, 66 (75%) had massive embolism without pre-existing additional cardiorespiratory disease, while 22 (25%) had significant cardiorespiratory disease in addition. 'Massive' embolism was defined as involvement of more than 50 per cent of the major pulmonary arteries and was assessed in 61 patients by pulmonary arteriography (Miller *et al.*, 1971), and at pulmonary embolectomy in 27 patients. All patients were referred for treatment from other hospitals.

Of the 88 patients, 85 had a clinically identifiable acute episode of massive embolism. Of these 85 patients, 35 were seen within 12 hours of the massive event, 45 were seen between 12 and 48 hours, and the remaining 5 were seen between 48 and 96 hours. Some of these 85 patients had episodes suggestive of minor pulmonary embolism with pulmonary infarction before the massive episode, but these never preceded the massive embolism by more than two weeks. The remaining 3 patients, all in the group with additional cardiorespiratory disease, had massive embolism with longer histories and no identifiable acute episode.

Sixteen deaths (18%) occurred during the initial admission, mainly as the result of intractable haemodynamic disturbance caused by massive embolism. Of the 72 surviving patients, 48 were women and 24 were men with an age range of 19 to 71 years (median 50 years) and form the basis of the subsequent discussion.

Cardiorespiratory disease, other than pulmonary embolism, was present in 17 of the 72 surviving patients. Previous myocardial infarction had occurred in 4, generalised left ventricular disease was present in 2, 1 patient had angina, another mitral stenosis, and a further patient had a large peripheral arteriovenous fistula. Three patients had systemic hypertension. Two patients had carcinoma of the bronchus, and 3 had obstructive airways disease.

The predisposing factors to the development of massive pulmonary embolism included operation (for benign and neoplastic disease) or trauma (46 patients), bed-rest (4 patients), oral contraceptives (3 patients), pregnancy (2 patients), recent myocardial infarction (2 patients), mitral stenosis, carcinoma of bronchus, lymphosarcoma, ulcerative colitis, and nephrotic syndrome (1 patient with each). Ten patients had no obvious predisposing factor.

Treatment

Treatment of patients with acute massive pulmonary embolism has varied over this 9-year period. In the early years, most patients were treated by pulmonary embolectomy, but later many patients were treated with a thrombolytic agent streptokinase (Kabikinase)* or with heparin. The results of these treatment regimens have been reported elsewhere (Paneth, 1967; Miller *et al.*, 1971; Tibbutt *et al.*, 1974; Miller *et al.*, 1977). Some patients were initially treated with streptokinase and subsequently by embolectomy because of deterioration, and others initially by heparin and then by streptokinase or embolectomy because of deterioration.

The final treatment used in the 72 surviving patients was embolectomy (33 patients), streptokinase (31 patients), and heparin (8 patients).

The majority of patients leaving hospital were treated with anticoagulants (warfarin) for 3 to 6 months. Thirteen patients were kept on long-term oral anticoagulants.

Operations to interrupt the venous system of the legs or the inferior vena cava were not carried out in any of these surviving patients.

Causes of late death

There were 5 late (after initial hospitalisation) deaths (9%) in the 55 patients without other cardiorespiratory disease. Malignant disease (carcinoma of the cervix, carcinoma of the breast, reticulum-cell sarcoma, and carcinoma of the rectum) accounted for 4 deaths. The patient who died of carcinoma of the rectum was the only one of these patients known to have malignant disease at the time of massive pulmonary embolism; surgery, trauma, and pregnancy were the identifiable predisposing factors in the other 3 patients who later died of neoplastic disease. One patient in whom the initial predisposing factor for pulmonary embolism was immobility, died suddenly 30 months after initial treatment. Necropsy was not carried out on this patient; the clinical circumstances suggested acute myocardial infarction, but the possibility that death was caused by recurrent massive pulmonary embolism cannot be excluded.

Of the 17 patients with additional cardiorespiratory disease, 7 (41%) died 3 to 69 months after the initial embolism. Two died of carcinoma of the bronchus recognised at the time of pulmonary embolism. Three died of left ventricular failure; these were all patients with known left ventricular disease. One of these patients died 6 months after the initial embolus had been treated, and had both old and new pulmonary infarcts at necropsy. One patient with a long history of obstructive airways disease died of coronary artery disease with asthma and bronchitis contributing to her death. The seventh patient died suddenly 38 months after initial treatment for pulmonary embolism; the cause of death is unknown as a necropsy was not performed.

Scope of follow-up

Of the initial series of 88 patients, 16 died in hospital and 12 subsequently. Of the remaining 60 patients, 56 were traced and recalled for follow-up a minimum of 1 year after initial treatment. The duration of follow-up in these 56 patients is shown in Fig. 1. Patients who died during the follow-up period and the 4 who could not be traced are not included in Fig. 1. The median follow-up period was 5 years.

The history was taken with particular attention to symptoms of cardiopulmonary insufficiency such as dyspnoea and chest pain and to symptoms of recurrent pulmonary embolism such as pleurisy, haemoptysis, sudden dyspnoea, or collapse. Examination was directed to any clinical features suggestive of pulmonary hypertension, e.g. abnormal jugular venous pulse, praecordial pulsation,

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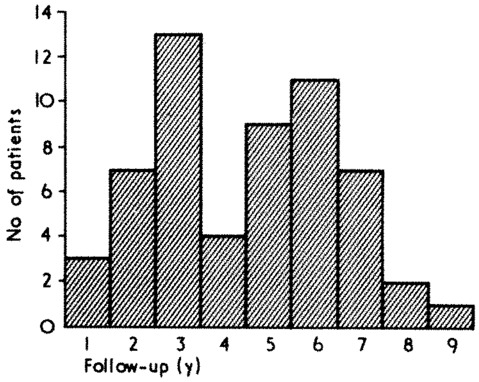

Fig. 1 *Duration of follow-up in 56 patients.*

or splitting of the second heart sound; to the intensity of the pulmonary component of the second heart sound; and to evidence of other cardiopulmonary abnormalities, e.g. systemic hypertension, left ventricular dysfunction, or obstructive airways disease.

A 12-lead electrocardiogram was taken and compared with the electrocardiogram taken at the time of pulmonary embolism. The plain posteroanterior chest radiograph was analysed for cardiothoracic ratio, size of main pulmonary artery, width of right descending pulmonary artery, areas of oligaemia, height of the diaphragm, linear and other shadows, and the presence of pleural thickening.

Finally, a perfusion lung scan was performed using ^{99m}Technetium-labelled macroaggregated albumin. Four views were obtained using a 3-inch single crystal detector. Abnormalities recorded were generalised reduction in one lung by comparison with the other, localised areas of underperfusion, and whether these were single or multiple. Quantification of lung scan abnormalities was not attempted, but the lung scan was compared with the chest *x*-ray film after each had been assessed separately.

Results of assessment

PATIENTS WITHOUT ADDITIONAL CARDIORESPIRATORY DISEASE

Of the 46 patients seen whose initial embolism was not complicated by additional cardiopulmonary disease, 31 (67%) were asymptomatic throughout the period of follow-up. Nine patients (20%) complained of mild exertional dyspnoea. Three patients had vague chest pains which were not pleuritic, one had an episode of bronchitis during the follow-up period, and one patient had vague chest pains and slight exertional dyspnoea. The only patient who had any history suggestive of recurrence of pulmonary embolism had an episode of pleurisy and haemoptysis 5 years after the initial episode and also complained subsequently of angina. This patient was investigated by cardiac catheterisation 6 years after the initial episode and was shown to have mild pulmonary hypertension (pulmonary artery systolic pressure 40 mmHg) without pulmonary arteriographic abnormalities, normal left heart pressures, and a normal coronary arteriogram.

Forty-one patients (89%) had no abnormal physical signs. Mild systemic hypertension was found in 3 patients. There was an ejection systolic murmur at the apex and a double apical cardiac impulse in one patient. One patient had an abnormal second heart sound with abnormally wide expiratory splitting increasing on inspiration: this patient did not have right bundle-branch block, nor was the pulmonary valve closure sound (P2) increased relative to the aortic valve closure sound (A2) on phonocardiography.

The electrocardiogram was normal in 38 patients (83%). T wave inversion in V1 to V4 was present in 3 patients, and 2 patients had an S_1 Q_3 T_3 pattern with inverted T waves in V1 to V4. All these abnormalities were also present in the electrocardiogram taken at the time of initial embolism. Complete right bundle-branch block was present in 2 patients: in one this was not initially present. One patient had an rsr^1 pattern in V1 present initially and at follow-up.

Perfusion lung scans were performed in 39 patients (85%) at the time of follow-up. Lung scan abnormalities are summarised in Table 1, 18 patients (46%) had normal scans.

At follow-up, 43 patients (93%) had chest *x*-ray film taken. Of these, 20 were normal (46%) and in 10 (23%) the only abnormalities were linear scars. The heart size was increased in 2 and the main pulmonary artery was enlarged (Fleischner, 1962) in 2 other patients. The width of the right descending pulmonary artery was normal in all.

In 5 patients, other chest *x*-ray abnormalities were seen: apical bullae were seen in 1, calcified tuberculous lymph nodes in 1, evidence of a lobectomy many years before in another, and scoliosis in 2. The remainder of the abnormalities, relevant to pulmonary embolism, are summarised in Table 2. These patients were classified as without additional cardiorespiratory disease since these abnormalities were usually minor, often not recognised at initial diagnosis of embolism, and did not result in cardiorespiratory dysfunction.

Table 1 *Results of perfusion lung scans*

	No. of patients	*Normal*	*Single defects*	*Multiple defects*	*General decreased perfusion one lung*	*General decreased perfusion one lung plus defect other lung*
Without additional cardiorespiratory disease	39	18 (46%)	7	7	5	2
With additional cardiorespiratory disease	9	2 (22%)	1	5	1	0
All patients	48	20 (42%)	8	12	6	2

Table 2 *Results of chest* x-*ray examination*

	No. of patients	*Normal*	*Oligaemia*	*Scars*	*Pleural shadows*	*Raised diaphragm*
Without additional cardiorespiratory disease	43	20 (46%)	1	17*	8	3
With additional cardiorespiratory disease	9	0	5	9†	2	1
All patients	52	20 (38%)	6	26	10	4

**Only* abnormality in 10.
†All patients had other abnormality.

PATIENT WITH ADDITIONAL CARDIORESPIRATORY DISEASE

Of the 10 patients seen at follow-up and who initially had additional cardiorespiratory disease, 4 were asymptomatic. Five had varying degrees of exertional dyspnoea, and 2 of these patients had chronic bronchitis with occasional acute exacerbations. Two patients had had episodes suggestive of recurrent pulmonary embolism and infarction with pleuritic chest pain and haemoptysis. These occurred 11 and 46 months after the initial embolic episode.

Only 2 of these patients were free of abnormal physical signs; 4 had a double apical impulse (or fourth heart sound), 3 had systemic hypertension, and 2 had expiratory wheeze. One patient had mitral stenosis with atrial fibrillation, while another had a peripheral arteriovenous fistula in the arm and a hyperdynamic circulation.

The electrocardiograms were normal in 5 patients. Left ventricular abnormalities (left bundle-branch block or ST-T changes) were present in 3, and 1 showed an old inferior myocardial infarct. In the patient with mitral stenosis the electrocardiogram showed atrial fibrillation and right ventricular hypertrophy.

Nine patients had a perfusion lung scan and this was normal in 2 patients (22%). The types and number of abnormalities seen are summarised in Table 1. The same 9 patients had chest *x*-ray films. All the radiographs were abnormal, and in no patient were scars the only defects. The heart size was increased in 4. The main pulmonary artery was enlarged in 1 patient with obstructive airways disease. The right descending pulmonary artery was abnormally large (17 mm) in another patient who had had a previous myocardial infarction, but was of normal size in the remaining patients. Chest *x*-ray films also showed evidence of old tuberculous infection and emphysema in 1 patient, emphysema alone in another, left atrial enlargement and upper lobe blood diversion in the patient with mitral stenosis, and upper lobe blood diversion in a patient with severe ventricular dysfunction from coronary artery disease. The abnormalities relating to pulmonary embolism are summarised in Table 2.

LATE CARDIAC CATHETERISATION STUDIES

Fourteen patients had right heart catheterisation and pulmonary arteriography 2 to 72 months after initial treatment. Of 9 patients without additional cardiorespiratory disease, only 1 had an abnormal pulmonary artery pressure (described above). Of 5 patients with additional disease, 2 had raised pulmonary artery pressures, 1 as the result of mitral stenosis, the other because of left ventricular disease.

Pulmonary arteriograms were entirely normal in 5 patients (including the 4 restudied more than 6 months after the acute event) and only minor abnormalities were seen in the other 9 patients studied earlier. Pulmonary arteriograms were scored[1] using the method described by Miller *et al.* (1971), and the results are shown in Fig. 2. Of the 14 patients recatheterised, 6 were patients who had shown little arteriographic improvement when restudied immediately after the initial treatment period.

Discussion

These results indicate a satisfactory long-term prognosis for patients surviving the initial episode of acute massive pulmonary embolism and who have been treated by pulmonary embolectomy, streptokinase, or heparin. This favourable long-term outcome contrasts with the immediate high mortality of massive pulmonary embolism. The patients described in this series were a selected group as they had survived long enough after the immediate impact of massive embolism to be transferred from one hospital to another.

LATE MORTALITY

The late mortality of patients with additional cardiopulmonary disease (41%, 7 of 17 patients) was higher than that of patients whose initial embolism was not associated with other cardiopulmonary disease (9%, 5 of 55 patients). Though the number of patients with additional disease is small, this difference in mortality is striking. It has been postulated (Murphy and Bulloch, 1968) that late deaths attributable to non-resolution or recurrence of pulmonary embolism may be more common in patients with additional cardiopulmonary disease. However, we did not find any evidence of an increased incidence of non-resolution or recurrence in these patients; the high mortality in these patients resulted from progression of the additional cardiopulmonary disease.

There was no definite evidence of late death resulting solely from new or unresolved pulmonary embolism in any patient. One patient dying of chronic left ventricular disease was found to have both old and new pulmonary infarcts at necropsy. This is known to be a common finding in patients dying from cardiac failure. There was one late, sudden death in each group of patients, the cause of which was not confirmed by necropsy. Though pulmonary embolism cannot be excluded as the cause of death in these 2 patients, the clinical circumstances in 1 case suggested myocardial infarction, and the other patient had had a myocardial infarct 4 years before.

The high incidence of venous thromboembolism in patients with neoplastic disease is well known, and this series emphasises this association. It is of interest that of the 6 patients dying 3 months to 7 years later, 3 were not known to have malignant disease when they presented with massive embolism. It is possible that occult neoplasia was an unknown, but important, predisposing factor to embolism in these patients.

There was nothing to suggest that the form of initial treatment (pulmonary embolectomy, streptokinase, or heparin) was related to the nature or incidence of late deaths.

RECURRENCE OF EMBOLISM

It has been thought that there is a high incidence of recurrence of embolism in treated and untreated patients. The Urokinase Pulmonary Embolism Trial (1973) showed an incidence of 15 to 19 per cent recurrent embolism within the first 2 weeks of beginning treatment with urokinase or heparin. This has not been our experience. During the initial hospital treatment period, only 2 of these patients (2%) had evidence of recurrence: 1 of these was the only patient in the entire series to have an operation on the inferior vena cava. Both these patients with early recurrence of embolism died during their initial admission, representing 13 per cent of all the hospital deaths in this series.

Although maintenance anticoagulants were seldom used, the incidence of clinically apparent recurrent pulmonary embolism over the period of follow-up was low. Three patients (18%) with additional cardiorespiratory disease had evidence of recurrence: 1 patient who died of left ventricular disease had small fresh pulmonary infarcts at

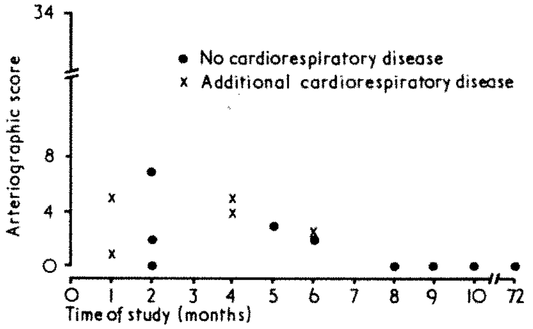

Fig. 2 *Late pulmonary arteriographic results.*

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[1] Severity of embolism is assessed in terms of both involvement of the main pulmonary arteries by clot and reduction in peripheral vessel perfusion. Reduction of perfusion is scored out of 18 and involvement of the pulmonary arteries by clot is scored out of 16. The scores for perfusion and involvement are added together to give a final score. Thus a normal arteriogram scores 0, while a final score of more than 17 indicates massive embolism.

necropsy, and 2 other patients had a history of pleurisy and haemoptysis 1 and 4 years after initial treatment. None of these patients was on anticoagulants at the time of recurrence. Only 1 patient without additional cardiorespiratory disease had symptoms suggestive of recurrence. This low incidence of recurrence may have been the result of the vigorous initial treatment causing rapid restoration of the pulmonary circulation towards normal, and consequently an early return of systemic perfusion towards normal, decreasing the chance of further venous thrombosis. Other series (Crane *et al.*, 1969) in which the patients were treated by heparin together with surgical procedure to the inferior vena cava or leg veins have shown a higher incidence of recurrent embolism, but there is little doubt that the majority of patients treated by embolectomy or thrombolytic drugs have more rapid restoration of the pulmonary circulation towards normal (Hirsh *et al.*, 1968; Miller *et al.*, 1971; Urokinase Pulmonary Embolism Trial, 1973). It is possible that patients with additional cardiorespiratory disease are more liable to recurrence of pulmonary embolism than those without, but the small number of such patients in this series does not permit comment on this aspect.

RESOLUTION OF PULMONARY EMBOLISM

This study does not attempt to assess the rate of resolution of treated pulmonary embolism. Comparative rates of early angiographic resolution produced by thrombolytic agents and heparin have been reported previously in other series (Urokinase Pulmonary Embolism Trial, 1973; Hirsh *et al.*, 1968) and for some of the patients in the present series (Miller *et al.*, 1971; Tibbutt *et al.*, 1974). In this study, we have looked particularly for evidence of non-resolution 1 to 8 years after the initial embolic episode. We have found little such evidence other than the frequent persistent lung scan abnormalities. Similar findings have been reported by Paraskos *et al.* (1973).

There was no clinical evidence of pulmonary hypertension in any patient. The electrocardiogram usually reverted to normal, though some patients retained abnormal features which were part of the right ventricular 'strain' pattern present at the time of embolism. Only 2 patients had unexplained enlargement of the main pulmonary artery on chest *x*-ray film though in both the width of the right descending pulmonary artery was normal. It could be argued that the methods used for the detection of pulmonary hypertension in the majority of patients (clinical history and examination, electrocardiogram (Flowers and Horan, 1972), and chest *x*-ray) are insensitive and hence we failed to diagnose mild pulmonary hypertension in all cases where it existed. The results of late cardiac catheterisation suggest that this is not so. Fourteen patients were restudied and 11 had normal pulmonary artery pressures. In 2 of the 3 patients with pulmonary hypertension, this resulted from proven left heart disease. Only 1 patient had mild unexplained pulmonary hypertension. This patient had a normal pulmonary arteriogram and the raised pulmonary artery pressure may have resulted from small vessel obstruction caused by the previous embolism or from an unrelated cause. The results of arteriography are particularly significant since 6 of these patients were restudied because of poor angiographic resolution immediately after initial therapy and might be considered to be the patients most likely to develop subsequent pulmonary hypertension.

Thus, this study does not lend any support to the suggestion that massive pulmonary embolism leads to chronic thromboembolic pulmonary hypertension. It must be remembered, however, that all the patients were vigorously treated: our experience does not deny the possibility that untreated massive pulmonary embolism could lead ultimately to chronic thromboembolic pulmonary hypertension.

The perfusion lung scan, and in a small number the pulmonary arteriogram, were used to judge the completeness of resolution of pulmonary embolism. The lung scan is a sensitive method of detecting areas of abnormal lung perfusion, but the interpretation and standardisation of scans is difficult. Tow and Wagner (1967) described a group of patients with 'severe' pulmonary embolism (31 to 50% of the lung involved), only 1 of whom had a completely normal lung scan at 2 months. The Urokinase Pulmonary Embolism Trial (1973) showed that approximately 75 per cent of lung scans had resolved in patients treated with urokinase or heparin at 1 year: the majority of these patients did not have massive embolism.

We have not attempted to quantify lung scans, but our findings in patients seen 1 to 9 years later show normal scans in 42 per cent. The remainder had varying abnormalities usually not more than slight, and sometimes corresponding to a scar or pleural thickening visible on chest *x*-ray film, raised diaphragm, or cardiac enlargement. More patients with additional cardiorespiratory disease had abnormal lung scans (76%) and chest *x*-ray films (100%) than patients without additional disease in whom 54 per cent of lung scans and 54 per cent of chest *x*-ray films were abnormal. This is not unexpected since these lung scan abnormalities may result from the associated disease rather than from pulmonary embolic disease and do not necessarily reflect non-resolution. There is no clear relation between completeness of resolution and initial treatment method (embolectomy or streptokinase).

The persistence of lung scan and, on occasion, electrocardiographic abnormalities is of obvious clinical significance when assessing a possible recurrence in a patient with a past history of pulmonary embolism.

Frequent minor pulmonary arteriographic abnormalities were seen in patients restudied within 6 months of initial treatment (Fig. 2). It is likely that resolution is not complete in some patients by 6 months. The results of perfusion lung scanning in a larger number of patients at a later date suggest that minor perfusion abnormalities may often persist for long periods or perhaps indefinitely. Such minor incomplete resolution does not seem to be responsible for any serious disturbance in the patient. We do not know whether such incomplete resolution, if followed for several decades, might eventually lead to chronic thromboembolic pulmonary hypertension.

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References

Crane, C., Hartsuck, J., Birtch, A., Couch, N. P., Zollinger, R., Matloff, J., Dalen, J., and Dexter, L. (1969). The management of major pulmonary embolism. *Surgery, Gynecology and Obstetrics*, **128,** 27–36.

Dalen, J. E., and Alpert, J. S. (1975). Natural history of pulmonary embolism. *Progress in Cardiovascular Disease*, **17,** 259–270.

Fleischner, F. G. (1962). Pulmonary embolism. *Clinical Radiology*, **13,** 169–182.

Flowers, N. C., and Horan, L. G. (1972). Subtle signs of right ventricular enlargement and their relative importance. In *Advances in Electrocardiography*, p. 297. Ed. by R. C. Schlant and J. W. Hurst. Grune and Stratton, New York.

Hirsh, J., Hale, G. S., McDonald, I. G., McCarthy, R. A., and Pitt, A. (1968). Streptokinase therapy in acute major pulmonary embolism: effectiveness and problems. *British Medical Journal*, **4,** 729–734.

Magidson, O., and Jacobson, G. (1955). Thrombosis of the main pulmonary arteries. *British Heart Journal*, **17,** 207–218.

Miller, G. A. H., Hall, R. J. C., and Paneth, M. (1977). Pulmonary embolectomy, heparin and streptokinase—their place in the treatment of acute massive pulmonary embolism. *American Heart Journal*, **93,** 568–574.

Miller, G. A. H., Sutton, G. C., Kerr, I. H., Gibson, R. V., and Honey, M. (1971). Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. *British Medical Journal*, **2,** 681–684.

Murphy, M. L., and Bulloch, R. T. (1968). Factors influencing the restoration of blood flow following pulmonary embolization as determined by angiography and scanning. *Circulation*, **38,** 1116–1126.

Paneth, M. (1967). The treatment of pulmonary embolism. *British Journal of Surgery*, **54,** 468–470.

Paraskos, J. A., Adelstein, S. J., Smith, R. E., Rickman, F. D., Grossman, W., Dexter, L., and Dalen, J. E. (1973). Late prognosis of acute pulmonary embolism. *New England Journal of Medicine*, **289,** 55–58.

Phear, D. (1960). Pulmonary embolism. A study of late prognosis. *Lancet*, **2,** 832–835.

Tibbutt, D. A., Davies, J. A., Anderson, J. A., Fletcher, E. W. L., Hamill, J., Holt, J. M., Lea Thomas, M., De J. Lee, G., Miller, G. A. H., Sharp, A. A., and Sutton, G. C. (1974). Comparison by controlled clinical trial of streptokinase and heparin in treatment of life-threatening pulmonary embolism. *British Medical Journal*, **1,** 343–347.

Tow, D. E., and Wagner, H. N. (1967). Recovery of pulmonary arterial blood flow in patients with pulmonary embolism. *New England Journal of Medicine*, **276,** 1053–1059.

Urokinase Pulmonary Embolism Trial (1973). *Circulation*, **47-48,** Suppl. 11.

Wood, P. (1956). *Diseases of the Heart and Circulation*, 2nd ed., p. 816. Eyre and Spotiswoode, London.

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Clinical course and late prognosis of treated subacute massive, acute minor, and chronic pulmonary thromboembolism

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Thirty-eight patients with pulmonary embolic disease, other than acute massive pulmonary embolism, have been assessed clinically and by right heart catheterisation and pulmonary arteriography or pulmonary embolectomy. In addition, complete follow-up information was obtained in 92 per cent (35) of patients 1 to 8 years after their initial illness. On the basis of the history and the pulmonary arteriographic appearances, three subgroups are described—subacute massive, acute minor, and chronic pulmonary embolism. Patients with subacute massive disease rarely had a well-defined predisposing factor to thromboembolism, had pulmonary arteriograms indistinguishable from acute massive embolism, but had long histories mainly of exertional dyspnoea which contrasts with the characteristically short, dramatic histories of patients with acute massive embolism. These patients had higher pulmonary artery pressures than patients with acute massive embolism. Patients with minor embolism usually had a well-defined predisposing cause to thromboembolism and normal haemodynamic findings. Patients with chronic embolism rarely had a well-defined predisposing factor to thromboembolism, had pulmonary arteriograms easily distinguishable from other forms of embolic disease, and had the highest pulmonary artery pressures.

The late prognosis of both acute minor and subacute massive embolism is good, recurrence of embolism is rare, and late pulmonary hypertension is not seen. In contrast, patients with chronic thromboembolic disease follow a progressively worsening course with persistent pulmonary hypertension, increasing right heart failure, and eventual death.

Pulmonary embolic disease has a wide variety of clinical presentations. The definition of subgroups facilitates the understanding of the clinical presentation, the haemodynamic disturbance, the natural history, and the effect of therapeutic interventions. The variables which are important in defining these subgroups are the severity of embolism, which can best be assessed by pulmonary arteriography; the duration of embolism, which can only be assessed from the history; and the presence or absence of additional cardiorespiratory disease other than pulmonary embolism.

We have defined four subgroups in terms of these variables; acute massive, subacute massive, acute minor, and chronic pulmonary embolism. Patients with acute massive pulmonary embolism present with a history of less than 48 hours' duration, have more than 50 per cent obstruction of major pulmonary arteries, and have usually had an acute episode of cardiovascular collapse. The clinical presentation of acute massive pulmonary embolism with and without additional cardiorespiratory disease, and the resultant haemodynamic disturbance, treatment, and long-term follow-up have previously been described (Sutton *et al.*, 1969; Miller and Sutton, 1970; Miller *et al.*, 1971; Miller *et al.*, 1977; Hall *et al.*, 1977).

This study is concerned with three further subgroups of patients with pulmonary embolic disease.

Subacute massive pulmonary embolism: These patients present with longer histories (more than 2 weeks) with no acute episode of collapse, but they have massive pulmonary embolism (greater than 50% obstruction of major pulmonary arteries) shown at pulmonary arteriography or embolectomy.

Acute minor pulmonary embolism: Patients with less than 50 per cent obstruction of major pulmonary arteries and who usually have short histories (less than 2 weeks).

Chronic pulmonary embolism: Patients who, when first seen, have abnormal pulmonary arteriograms with grossly diminished uneven pulmonary perfusion, not resulting from identifiable recent thrombus, and irregular pulmonary vessels, sometimes with clot adherent to their walls. These

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patients usually have long histories (several months, or even years).

Patients and diagnosis

The present series is made up of 38 consecutive patients with pulmonary embolic disease, other than acute massive embolism, referred for treatment at the Brompton Hospital between 1965 and 1973. None of these patients had other significant cardiorespiratory disease. The diagnosis of embolic disease was confirmed at pulmonary arteriography in 36 patients; in the remaining 2 patients, both of whom had subacute massive pulmonary embolism, the diagnosis was confirmed at embolectomy. Patients were divided into three groups, according to the length of their histories and the pulmonary arteriographic appearances. The main features of these three diagnostic groups are summarised in Table 1. Pulmonary arteriograms were scored (Miller *et al.,* 1971; Hall *et al.,* 1977), taking into account both involvement of major pulmonary arteries by thrombus and reduction of zonal flow. A theoretical score of 34 represents involvement of all major arteries by thrombus and total reduction of flow to all zones, while a score of 0 represents a normal pulmonary arteriogram. An arteriographic score of greater than 17 represents massive embolism. The method of late follow-up was as follows. Patients were recalled and examined by two of the authors. Particular notice was taken of symptoms or signs that might suggest pulmonary hypertension. A chest *x*-ray film, 12-lead electrocardiogram,and perfusion lung scan ($^{99\,m}$Technetium labelled albumin macroaggregates) were carried out.

Table 1 *Composition of three diagnostic groups and their treatment and mortality*

	Subacute massive	*Minor*	*Chronic*
Number of patients (female, male)	13 (7F, 6M)	17 (12F, 5M)	8 (6F, 2M)
Age (y)—Mean	45	43	49
Range	24–65	23–66	42–68
Duration of symptoms	2–12 w	1 d–2 w	3 w–5 y
Treatment of initial episode			
Heparin	2	12	0
Streptokinase	7	4	2
Embolectomy	4	0	0
Oral anticoagulants	0	1	6
Early deaths	4	1	0

Results

CLINICAL COURSE BEFORE DIAGNOSIS

The 13 patients with subacute massive pulmonary embolism had symptoms for longer than 2 weeks. The most frequent symptom was progressively increasing dyspnoea, with decreasing effort tolerance (8 patients), often associated with episodes of pleuritic chest pain (7 patients), and haemoptysis (4 patients). No patient had an isolated episode of cardiovascular collapse. These symptoms contrast with those of patients with acute massive pulmonary embolism (Hall *et al.,* 1977), in whom the history was short, with an episode of cardiovascular collapse. The 17 patients with minor embolism had shorter histories (up to 2 weeks), and complained of pleuritic chest pain (15 patients), haemoptysis (4 patients), and dyspnoea (3 patients). In the 8 patients with chronic thromboembolic pulmonary hypertension, the history was usually much longer, and in 6 patients, ranged between 6 months and 5 years. Two patients, however, had shorter histories: one patient had pleuritic pain for 3 weeks, and the other had 6 weeks of progressive dyspnoea. These patients with shorter histories had similar aterio-graphic findings to the other 6 patients. Of the 6 patients with long histories, 5 had suffered from progressive dyspnoea and decreasing exercise tolerance and only 1 had had recurrent episodes of pleuritic chest pain.

PREDISPOSING FACTORS

The majority of patients (14 of 17=82%) with minor pulmonary embolism had well-defined factors predisposing to the development of thromboembolic disease, for example, recent surgery (8 patients), trauma (4 patients), and oestrogen/progesterone contraceptive preparations (2 patients). In contrast, only 4 of the 13 patients (31%) with subacute massive pulmonary embolism had a well-defined predisposing cause for thromboembolism (oral contraceptives). No patient with chronic thromboembolic disease had a well-defined predisposing factor.

PULMONARY ARTERIOGRAPHY AND EMBOLECTOMY FINDINGS

The mean initial arteriographic scores for each group are shown in Table 2. All patients with minor embolism had fresh thrombus in the pulmonary arteries (Fig. 1). Though the clinical course of patients with subacute massive pulmonary embolism was very different from that of patients with acute massive pulmonary embolism, the pulmonary arteriographic appearances in 8 of the patients with subacute massive pulmonary emboli and the embolectomy findings in 1, were those of fresh thrombus in the pulmonary arteries, indistinguishable from the appearances seen in patients with acute massive pulmonary embolism (Fig. 2). Three patients in the subacute massive pulmonary embolism group had arteriographic evidence of both old adherent thrombus and new free thrombus, and the remaining patient had mainly new thrombus causing the pulmonary artery obstruction, but also some slight narrowing of a few pulmonary arteries without definite evidence of old thrombus. All patients with chronic thromboembolic pulmonary hypertension had strikingly abnormal pulmonary arteriograms (Fig. 3). None had evidence of new thrombus in the pulmonary arteries, but 2 patients had old adherent thrombus. In all, the most conspicuous abnormality was gross uneven narrowing of major pulmonary arteries; this abnormality did not occur in any patient with subacute or minor pulmonary embolism.

HAEMODYNAMICS

Pulmonary artery systolic and mean pressure in each group differed significantly from all other groups, and in minor pulmonary embolism were not significantly different from normal (Table 2).

CLINICAL COURSE DURING INITIAL HOSPITAL ADMISSION

The treatment received by each group of patients during their hospital stay is shown in Table 1. The number of patients receiving each treatment is too small to assess the relative merits of the different forms of treatment used. There were no early hospital deaths in the chronic group; treatment with streptokinase infusion was attempted in two of these patients, in whom the pulmonary arteriogram showed old adherent thrombus as well as grossly uneven pulmonary vessels, but this treatment did not alter arteriographic appearances, or lower the pulmonary artery pressure. One patient in the minor group, who had an initial arteriographic index of 15, died from a brain-stem haemorrhage while receiving streptokinase.

Four patients in the subacute massive pulmonary embolism group were treated by pulmonary embolectomy. One patient, seen early in the series, had pulmonary embolectomy as the initial treat-

Table 2 *Results of pretreatment right heart catheterisation and pulmonary arteriography (mean ±SEM)*

	N	*Pulmonary artery systolic pressure (mmHg)*	*Pulmonary artery mean pressure (mmHg)*	*Pulmonary arteriogram severity index*
Minor	17	28·4 ±2·1†	19·0 ±1·5†	9·5 ±1·0†
Acute massive*	42	41·0 ±1·2†	28·0 ±0·75†	24·6 ±0·4
Subacute massive	11	54·0 ±5·0†	35·0 ±3·0†	21·8 ±1·1
Chronic	8	85·2 ±5·7†	48·0 ±2·2†	20·9 ±1·0

*These patients are those with acute massive pulmonary embolism but without cardiorespiratory disease described by Hall *et al.* (1977), and are included for comparison.

†Denotes that this group is significantly different (P < 0·05) from each of the three other groups (unpaired t test).

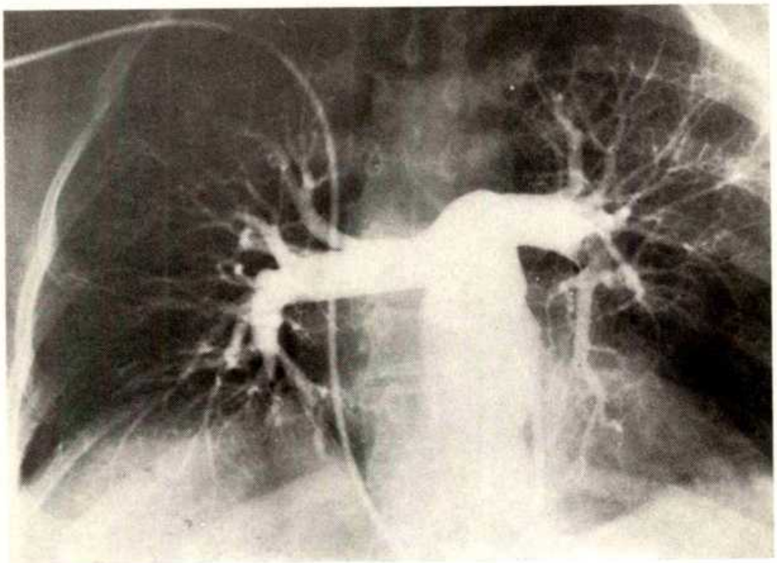

Fig. 1 *The pulmonary arteriogram of minor embolism. The embolism involves less than 50 per cent of the pulmonary arteries.*

ment. This patient suffered a cardiac arrest at the induction of anaesthesia, and we now recognise this to be an avoidable complication (Miller *et al.*, 1977). It is unlikely that we would now recommend surgery for such a patient, but would give either streptokinase or heparin infusion. Two patients who showed little arteriographic improvement after 6 and 8 days of heparin treatment were subjected to embolectomy. Both survived the operation, but one died of a fatal recurrent embolism a week after the operation. We would not now recommend pulmonary embolectomy for either of these patients. The fourth patient was treated by embolectomy because of severe gastrointestinal bleeding during heparin therapy. This patient, unfortunately, died during the operation, but we

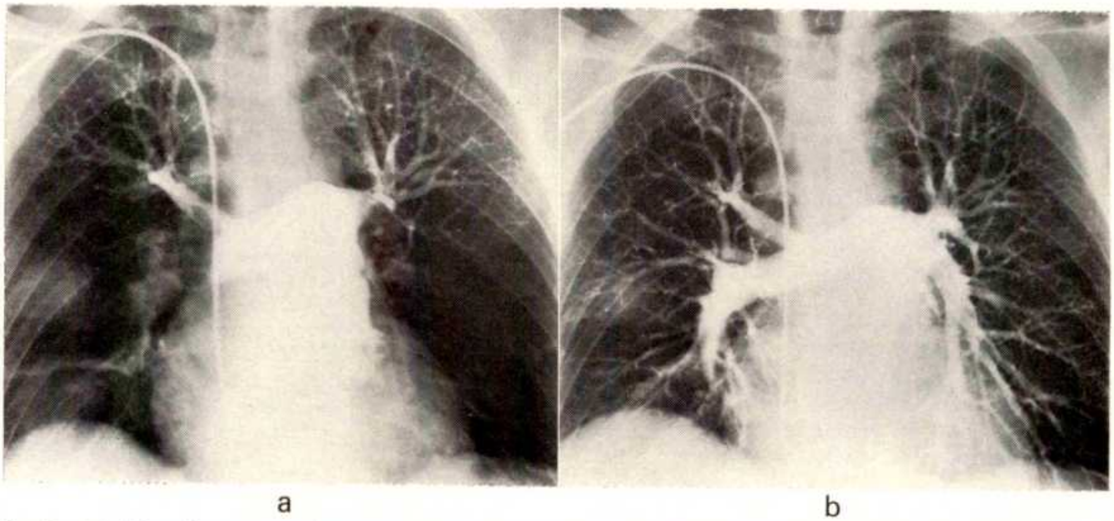

Fig. 2 *(a) The pulmonary arteriogram of subacute massive embolism. The embolism involves more than 50 per cent of the pulmonary arteries. (b) The same patient 3 days later, after treatment with streptokinase. The response is similar to acute massive pulmonary embolism.*

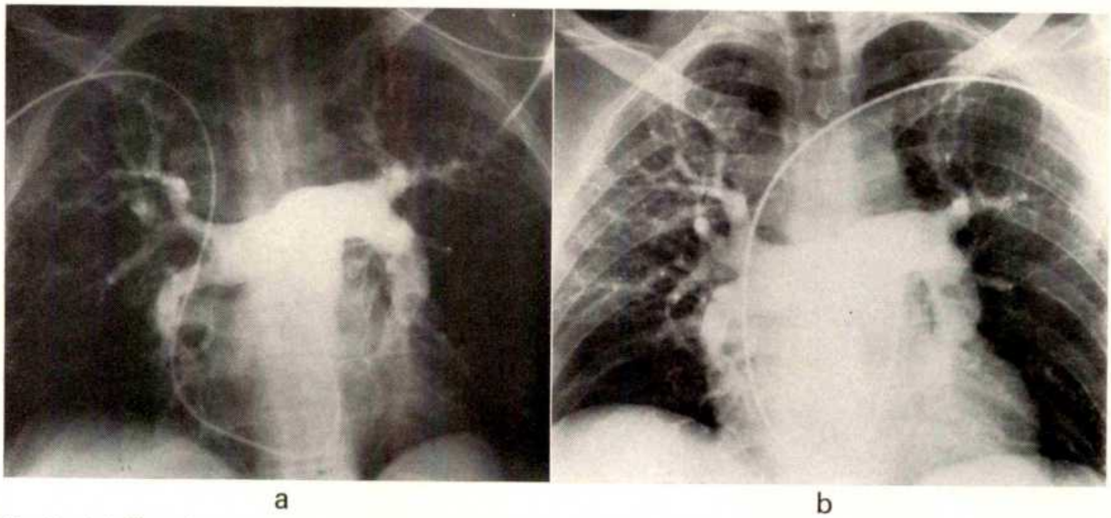

Fig. 3 *(a) The pulmonary arteriogram of chronic embolism. (b) The same patient 3 years later. The appearances remain those of chronic pulmonary embolism though slight alteration has occurred at the bifurcation of the right pulmonary artery.*

would recommend embolectomy if faced with such a patient again. Therefore, of the 3 deaths in patients who had pulmonary embolectomy, 2 were directly related to the operation, and 1 of these 2 was probably avoidable in the light of our current knowledge.

LATE FOLLOW-UP

Complete follow-up was obtained for 35 of the original 38 patients (92%). Details and duration of follow-up in the 33 patients who survived initial treatment are summarised in Table 3. The clinical course of the patients originally diagnosed as having chronic thromboembolic pulmonary hypertension was very different from that of the other two groups. Four (50%) of these patients died during the follow-up period, and 3 of these deaths resulted from progressive right ventricular failure. The fourth patient died elsewhere during an attempted surgical clearance of the pulmonary arteries. No patient in this group, surviving or dead, had clinically identifiable recurrent pulmonary embolism or infarction during the follow-up period. Of the 4 patients who survived to follow-up, 3 had severe dyspnoea and fatigue on exertion, and the same 3 patients had physical signs of pulmonary hypertension and electrocardiographic evidence of right ventricular hypertrophy. The fourth survivor (case 7 in Table 5) was totally asymptomatic and had a normal electrocardiogram. All 4 survivors in this group had grossly abnormal perfusion lung scans with multiple perfusion defects (Fig. 4). Similar findings have been shown in perfusion scans in patients with chronic thromboembolic disease by Wilson *et al.* (1973). The chest *x*-ray films of all patients in the chronic group showed enlarged main and right pulmonary arteries and cardiomegaly (Table 4). Late pulmonary arteriograms and right heart catheterisations in 2 patients, including case 7 who was asymptomatic (Table 5), showed that the arteriographic index of severity had fallen while pulmonary hypertension remained unaltered. The significance of the changes in the severity index are uncertain, since it is extremely difficult to assess this index accurately in this group of patients.

The clinical course of patients with minor and subacute massive pulmonary embolism during the follow-up period was strikingly different from that seen in patients with chronic disease. There were no late deaths in either group resulting from thromboembolic disease. There was one late death in each group from malignant disease; in neither case was this evident at the time of the initial illness. Three patients, all in the minor group, had episodes of pleuritic chest pain, one associated with haemoptysis, possibly caused by a recurrent embolism. These occurred 1, 2, and 5 years after the initial episode. At follow-up, 2 of these patients had normal lung scans and chest *x*-rays, and the third, case 3 (Table 5), had a normal pulmonary arterio-

Table 3 *Details of late deaths and follow-up (follow-up was 92 per cent)*

	Subacute massive	*Minor*	*Chronic*
Survivors of initial episode	9	16	8
Late death	1	1	4
Lost to follow-up	1	2	0
Seen at follow-up	7	13	4
Duration of follow-up (y)			
Median	3	5	3, 4, 5 and 7
Range	1–6	1–8	

Table 4 *Results of perfusion lung scans and chest* x-*rays at follow-up*

	Subacute massive	*Minor*	*Chronic*
Lung scans (no.)	6	12	4
Normal	2	8	0
Single perfusion defect	2	2	0
Multiple perfusion defects	2 (33%)	2 (17%)	4 (100%)
Chest x-rays (no.)	7	13	4
Enlarged main or right pulmonary artery (17 mm)	0	0	4 (100%)

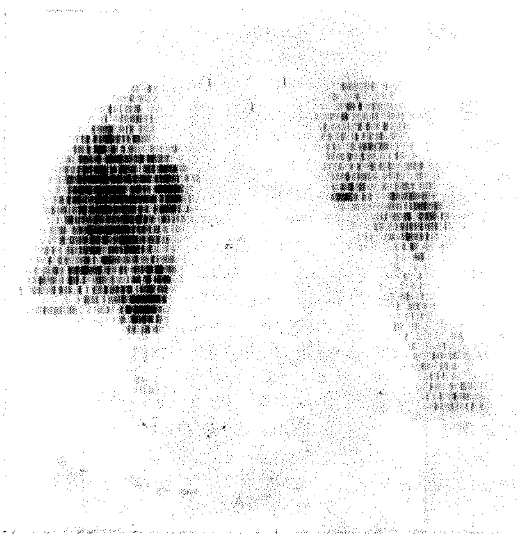

Fig. 4 *The perfusion lung scan of the same patient as Fig. 3, with chronic pulmonary embolism.*

Table 5 *Results of late cardiac catheterisation and pulmonary arteriography*

	Pulmonary artery systolic pressure (mmHg)			*Pulmonary arteriogram severity index*			*Interval between early and late studies (mth)*	*Lung scan follow-up*
	1	*2*	*3*	*1*	*2*	*3*		
Subacute massive								
Case 1	55	38	30	25	23	5	4	M
Case 2	75	44	35	28	19	0	5	N
Minor								
Case 3	55	34	23	16	10	0	5	—
Case 4	31	24	22	14	16	1	2	N
Case 5	30	21	23	4	9	0	11	N
Chronic								
Case 6	66	—	65	21	—	12	24	M
Case 7	70	—	70	23	—	15	84	M

The pulmonary artery pressures and arteriographic scores in the 7 patients in whom late cardiac catheterisation and pulmonary arteriography were performed.
Investigation 1, pretreatment; 2, immediately after initial treatment; 3, late study.
Lung scans were performed at follow-up (N, normal; M, multiple perfusion defects).

gram with normal right heart pressures and a normal chest *x*-ray film. No patient developed pulmonary hypertension during the period of follow-up, as assessed by physical signs, chest *x*-ray films, or electrocardiograms, or had developed significant cardiorespiratory symptoms. Late right heart catheterisation and pulmonary arteriography were performed mainly in patients who had shown a poor response to initial therapy. Despite this, pulmonary hypertension resolved and pulmonary arteries cleared in these patients (Table 5). One patient in the subacute massive group had a slightly raised pulmonary artery pressure, and the other, minor residual pulmonary arteriographic abnormalities. Persistent lung scan abnormalities were common in these two groups at follow-up. The lung scans of 8 of the 18 patients showed either single or multiple perfusion defects (Table 4).

Some patients with minor or subacute massive pulmonary embolism also had persistently abnormal electrocardiograms. One patient in the minor group had an abnormal electrocardiogram (right bundle-branch block and left axis deviation) and this abnormality was present at the time of his initial hospitalisation 3 years previously. Three patients in the subacute massive pulmonary embolism group had abnormal electrocardiograms. One patient had T wave inversion in leads V1–3, another patient in leads V1–6, and the third patient had a persistent $S_1Q_3T_3$ pattern and persistent T wave inversion in leads V1–3. In all 3, these changes were part of the electrocardiographic abnormalities seen during the initial illness.

Discussion

Although most clinicians are familiar with patients who present with subacute massive pulmonary embolism, the haemodynamic consequences and arteriographic appearances of this group have not been described previously, or contrasted with those of other forms of pulmonary embolic disease. These patients had pulmonary artery, systolic, and mean, pressures which were significantly higher than those in a group of patients with acute massive pulmonary embolism, in whom the extent of pulmonary artery obstruction was essentially the same. The mean systolic and pulmonary artery pressures of subacute massive pulmonary embolism were significantly lower than those of a group of patients with chronic thromboembolic pulmonary hypertension, in whom the extent of pulmonary artery obstruction was similar (Table 2). These findings suggest that the subacute course of pulmonary artery obstruction allows the right ventricle time to adapt to the increased load and to generate a higher pressure than it can achieve when acutely stressed. In chronic thromboembolic disease with long-standing obstruction to right ventricular ejection, the right ventricle generates even higher systolic pressures.

The main object of this and our previous study (Hall *et al.*, 1977) was to assess the incidence of serious long-term sequelae in patients with documented pulmonary embolic disease. We were particularly interested to know if recurrence and non-resolution were common and how often chronic thromboembolic pulmonary hypertension developed. In our previous study, which concerned the patients with acute massive pulmonary embolism, we found that recurrence and non-resolution were rare, and did not find evidence of chronic thromboembolic pulmonary hypertension in any of the 56 survivors, despite a follow-up period ranging from 1 to 9 years (median 5 years). These patients with acute massive embolism and those with minor embolism described here usually had well-defined predisposing factors to the development of thromboembolic disease, which were later eliminated, and short histories. They received energetic treatment early in their illness. Therefore, it is perhaps not surprising that they should have a good prognosis if they survive the initial embolism. This was not true of the patients with subacute massive embolism, since many of these patients had no identifiable predisposing cause, long histories, and started treatment relatively later in the course of their disease. These patients were, therefore, of great interest, since they might be expected to be at particular risk of non-resolution and late pulmonary hypertension. Yet, in spite of these adverse factors, we found no evidence that the late prognosis was any worse in these patients than in those with acute massive or minor embolism.

Our finding of a poor prognisis in chronic thromboembolic disease is in agreement with several previous reports (Fowler *et al.*, 1966; Goodwin *et al.*, 1963; Fleischner, 1967). Our finding of a good long-term prognosis in all other groups of pulmonary embolism is in agreement with Paraskos *et al.* (1973) who also studied the late prognosis of arteriographically documented pulmonary embolism. These authors noted only one late death from pulmonary hypertension, and this patient in their series undoubtedly had chronic embolic disease when first seen. In contrast with these favourable results, Phear (1960) found that serious symptoms, often related to chronic thromboembolic disease, were frequently found after acute embolism of all types, while deSoyza and Murphy (1972) reported that mild pulmonary hypertension was often found at late follow-up in patients who had suffered acute pulmonary embolism. Though these findings seem contradictory, it must be remembered that Phear studied patients in whom the diagnosis was established without the aid of cardiac catheterisation or pulmonary arteriography, and many of the patients subsequently developing symptoms may well have had chronic thromboembolic disease when first seen. In contrast, the diagnosis was confirmed in all our patients with minor, subacute massive, and acute massive pulmonary embolism by pulmonary arteriography or at pulmonary embolectomy, and consequently, patients who had chronic thromboembolic disease were not included in these diagnostic categories. Our patients with chronic embolism, who have been shown to have a poor prognosis, were often referred with a diagnosis of acute embolism, and the true diagnosis was established only by careful history taking and pulmonary arteriography. These patients with chronic disease might have been grouped with the others had not the diagnosis of chronic embolism been established by this process. If this separation had not been made, our results might have been similar to those of Phear. The findings of deSoyza and Murphy (1972) are more difficult to compare, since, though they state that pulmonary embolism was arteriographically documented, the arteriographic findings were not described. Their patients also showed frequent recurrence of embolism.

Paraskos *et al.* (1973) attributed the satisfactory prognosis to long-term anticoagulation and inferior vena caval ligation, both of which were frequently employed in their series. We cannot comment on the role of anticoagulation for several months after the acute event, since we do not have a control group in which this treatment was not employed. The results in our patients do, however, show that inferior vena caval ligation is not necessary to prevent either the recurrence of embolism or the development of chronic thromboembolic pulmonary hypertension.

Although the prognosis of all our patients other than those with chronic thromboembolism was good, patients with both minor and subacute massive pulmonary embolism, as well as patients with acute massive embolism (Hall *et al.*, 1977), frequently had abnormal perfusion lung scans at follow-up. This suggests that permanent obstruction to small vessels in the lungs has occurred, though the large pulmonary vessels have cleared: the arteriographic appearances at follow-up confirm normal large pulmonary vessels. The absence of serious symptoms or pulmonary hypertension suggests that small vessel damage is not of poor prognostic significance, at least over the first 5 to 10 years. The fact that lung scan and electrocardiographic abnormalities may persist must be remembered when attempting to make a diagnosis of recurrent pulmonary embolism, particularly if previous records are not available.

Although we have not observed chronic thromboembolic pulmonary hypertension develop in any of our patients, we need to ask whether this disease occurs as a result of unresolved pulmonary emboli. Clinical evidence and experience suggest that it can (Goodwin *et al.*, 1963; Fowler *et al.*, 1966; Fleischner, 1967); however, its development as a result of embolism proven at angiography in an initially normal pulmonary vasculature has not been documented. The possible reasons for this and why we have not observed it are numerous. Chronic thromboembolic pulmonary hypertension is a rare disease (Owen *et al.*, 1953) whereas acute pulmonary embolism is common, and, therefore, chronic embolism can only occur in an extremely small number of patients who have had acute embolism.

Chronic thromboembolic pulmonary hypertension is nearly always diagnosed late in its course, when pulmonary vascular obstruction is severe, as in our 8 patients, and the preceding embolic episodes are often so minor that they did not attract attention, or are wrongly diagnosed as other chest disease (Fleischner, 1967). Therefore, its development is not documented because symptoms warranting investigation did not occur until the disease was well advanced. Though this may be the sequence of events in some cases of chronic thromboembolic pulmonary hypertension, there has been a tendency to ascribe these cases of pulmonary hypertension to embolism (Blount, 1967) and other possible mechanisms have been ignored. A considerable number of patients in every series with this disease (Goodwin *et al.*, 1963; Fowler *et al.*, 1966), as well as in the present group, have not shown any clinical evidence at any time of the presumed causative emboli. In view of our failure to find this complication at follow-up of proven embolic disease, the possibility exists that at least some cases of chronic thromboembolic pulmonary hypertension result from thrombosis in abnormal pulmonary arteries rather than from embolism.

Whatever may be the aetiology of chronic thromboembolic pulmonary hypertension, occasional patients have been noted to improve on long-term anticoagulant therapy (Goodwin *et al.*, 1963; Wilhelmsen *et al.*, 1972). Though we did not see clinical improvement in our chronic patients, it is essential that the diagnosis of chronic thromboembolic pulmonary hypertension be confirmed by arteriography and anticoagulant treatment initiated since this is the only available treatment which may occasionally help to prevent the progression of this disease.

The division of patients with pulmonary embolic disease into the subgroups described helps in the understanding of the wide range of clinical presentations and haemodynamic disturbances that may occur as a result of pulmonary embolism. The long-term prognosis of patients surviving treated minor or subacute massive embolism is good, in contrast to the poor prognosis of patients with chronic thromboembolic pulmonary hypertension.

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References

Blount, S. G. (1967). Primary pulmonary hypertension. *Modern Concepts of Cardiovascular Disease*, **36**, 67–72.
deSoyza, N. D. B., and Murphy, M. L. (1972). Persistent post-embolic pulmonary hypertension. *Chest*, **62**, 665–668.
Fleischner, F. G. (1967). Recurrent pulmonary embolism and cor pulmonale. *New England Journal of Medicine*, **276**, 1213–1220.
Fowler, N. O., Black-Schaffer, B., Scott, R. C., and Gueron, M. (1966). Idiopathic and thromboembolic pulmonary hypertension. *American Journal of Medicine*, **40**, 331–345.
Goodwin, J. F., Harrison, C. V., and Wilcken, D. E. L. (1963). Obliterative pulmonary hypertension and thromboembolism. *British Medical Journal*, **1**, 701–711.
Hall, R. J. C., Sutton, G. C., and Kerr, I. H. (1977). Long-term prognosis of treated acute massive pulmonary embolism. *British Heart Journal.*, **39**, 1128–1134.
Miller, G. A. H., Hall, R. J. C., and Paneth, M. (1977). Pulmonary embolectomy, heparin and streptokinase—their place in the treatment of acute massive pulmonary embolism. *American Heart Journal*, **93**, 568–575.
Miller, G. A. H., and Sutton, G. C. (1970). Acute massive pulmonary embolism. Clinical and haemodynamic findings in 23 patients studied by cardiac catheterization and pulmonary arteriography. *British Heart Journal*, **32**, 518–523.
Miller, G. A. H., Sutton, G. C., Kerr, I. H., Gibson, R. V., and Honey, M. (1971). Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. *British Medical Journal*, **2**, 681–684.
Owen, W. R., Thomas, W. A., Castleman, B., and Bland, E. F. (1953). Unrecognized emboli to the lungs with subsequent cor pulmonale. *New England Journal of Medicine*, **249**, 919–925.
Paraskos, J. A., Adelstein, S. J., Smith, R. E., Rickman, F. D., Grossman, W., Dexter, L., and Dalen, J. E. (1973). Late prognosis of acute pulmonary embolism. *New England Journal of Medicine*, **289**, 55–62.
Phear, D. (1960). Pulmonary embolism. A study of late prognosis. *Lancet*, **2**, 832–835.
Sutton, G. C., Honey, M., and Gibson, R. V. (1969). Clinical diagnosis of acute massive pulmonary embolism. *Lancet*, **1**, 271–273.
Wilhelmsen, L., Hagman, M., and Werkö, L. (1972). Recurrent pulmonary embolism—incidence, predisposing factors and prognosis. *Acta Medica Scandinavica*, **192**, 565–575.
Wilson, A. G., Harris, C. N., Lavender, J. P., and Oakley, C. M. (1973). Perfusion lung scanning in obliterative pulmonary hypertension. *British Heart Journal*, **35**, 917–930.

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Nomogram for calculation of left ventricular volumes

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A nomogram has been devised for the rapid derivation of left ventricular volumes from single-plane angiograms obtained in the 30° right anterior oblique projection. The left ventricular volumes are derived from the use of the area-length formula of Dodge. The computed left ventricular volumes may then be adjusted to correspond to the actual volumes by an appropriate conversion chart.

Single-plane cineangiography in the right anterior oblique projection has been proposed as a technically easier method of obtaining the left ventricular volume than biplane angiography (Kasser and Kennedy, 1969; Snow *et al.*, 1969; Kennedy *et al.*, 1970). This paper presents a nomogram for the rapid derivation of the left ventricular volume from the right anterior oblique angiogram using a modified area-length formula of Dodge *et al.* (1960). It is hoped that this nomogram will prove useful in those medical centres where computers and light-pen writers might not be readily available. This nomogram could also serve as an independent means of rapidly performing or rechecking a large number of calculations involving corrected left ventricular volumes.

Principle

(a) CALCULATION OF LEFT VENTRICULAR VOLUME

The principle of the nomogram (Fig. 1) is based on the formula of an ellipsoid: $V' = 4/3\ \pi\ abc$,

where

V' = volume in cm^3

a = semi-major axis = one half length from apex to middle of aortic valve = 1/2 L cm.

b = semi-minor axis in right anterior oblique view (cm).

c = other semi-minor axis at right angles to b (not seen in right anterior oblique view).

If it is assumed that the left ventricle is shaped like a prolate spheroid (Dodge *et al.*, 1960) then $b = c$ and $V' = 4/3\ \pi\ ab^2$ . . . (1)

The projection of a prolate spheroid in 30° right anterior oblique view is assumed to be an ellipse (area = A cm^2) (Dodge *et al.*, 1960).

Then $A = \pi\ ab$ . . . (2)

Substituting for b in (1) from (2) and letting $L = 2a$

we get $V' = \dfrac{0{\cdot}848A^2}{L}$ . . . (3)

The volume V′ from equation 3 is then adjusted for the magnification of the *x*-ray film by using a linear correction factor M ($\geqslant 1$) where 1 cm true length = M cm on *x*-ray film as viewed or projected. Hence the computed volume V becomes

$V = \dfrac{0{\cdot}848A^2}{LM^3}$ . . . (4)

Equation (4) was used to compute the volume (end-diastolic or end-systolic) depicted in the nomogram in Fig. 1.

This computed volume V can be adjusted to correspond to the actual left ventricular volume (V_{corr}) as determined by models and post-mortem left ventricles of known volumes (Dodge 1971), using the Dodge equation

$V_{corr} = 0{\cdot}81\ V + 1{\cdot}9$ . . . (5).

The value of V_{corr} corresponding to V can then be read directly from the conversion scale V-V_{corr} on the extreme right-hand side of the nomogram.

Application

TO FIND LV VOLUME (RIGHT ANTERIOR OBLIQUE VIEW) (Fig. 2)

With the sharp point of a pencil, mark the length on line L and the magnification factor on line M. Join these two points with a straight line to cross the unscaled line G. By joining the point so obtained on line G and the planimetered area on line A a straight line may be extended to meet line V yielding the volume (cm^3).

If a grid is used to obtain the magnification factor where 1 cm^2 actual area corresponds to M^2 cm^2 *x*-ray distorted area (i.e. M^2 = *x*-ray distorted area/

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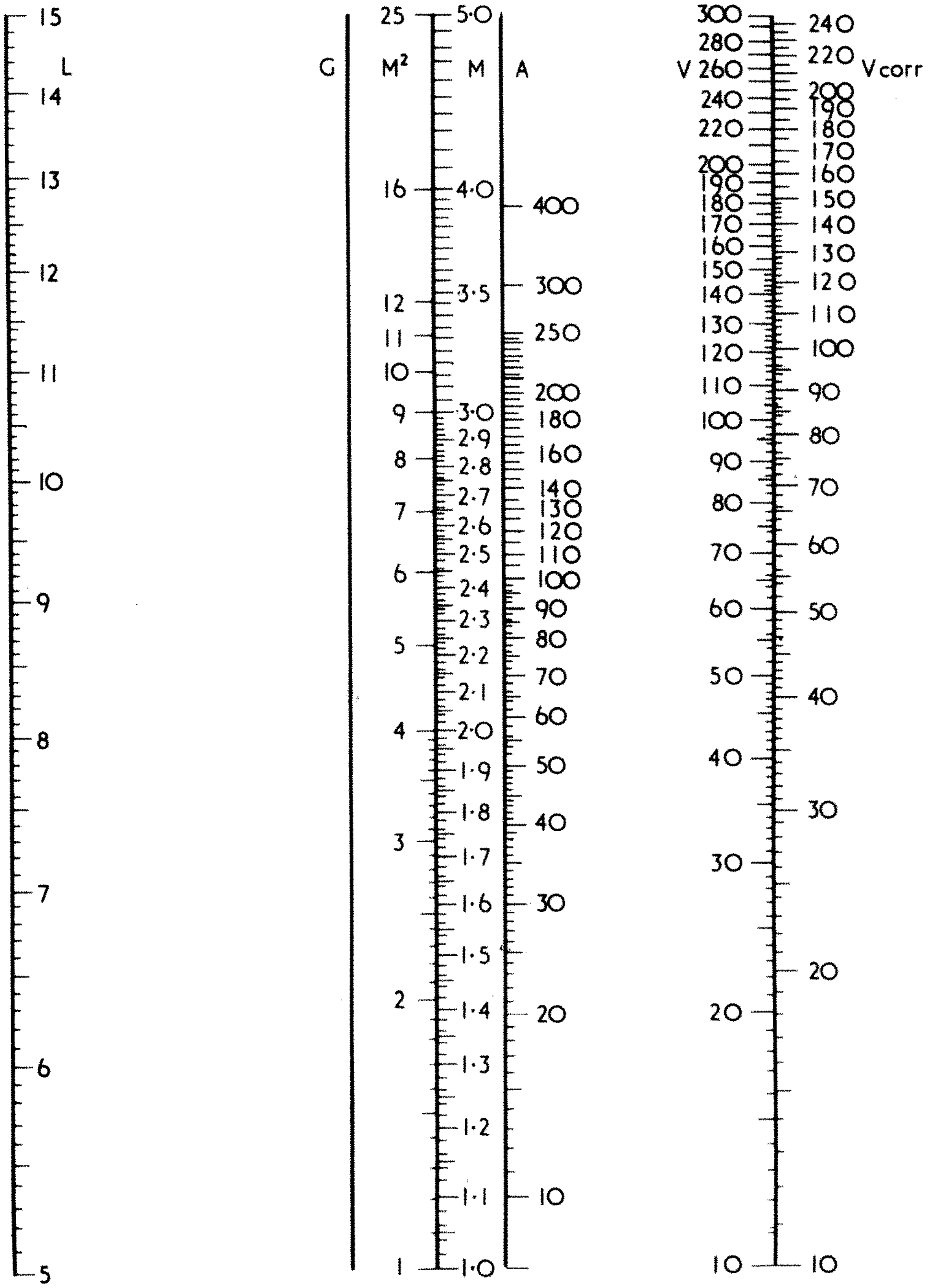

Fig. 1 *Nomogram for estimation of left ventricular volume: L = length (cm) as measured from apex to midpoint of aortic valve in 30° RAO view; M = linear magnification factor; M² = area magnification factor when a grid is used; A = LV planimetered area in 30° right anterior oblique (cm²); V = computed volume (cm³); Vcorr = corrected volume (cm³).*
A straight line joining L and M (or M²) intersects the unscaled line G. A second straight line drawn between the point on G and the observed area is extended to V to obtain the computed or corrected volume.

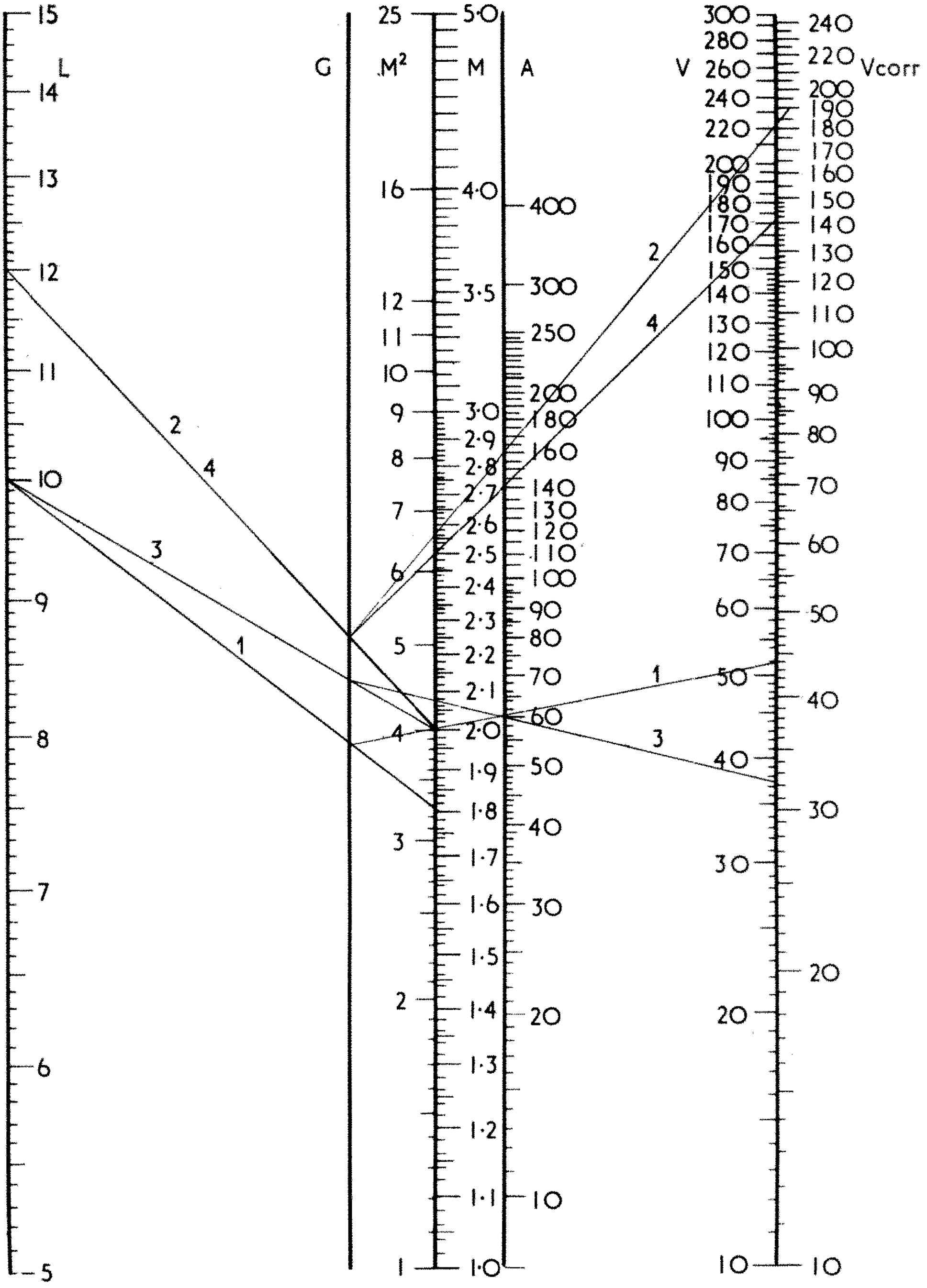

Fig. 2 *Illustrated use of nomogram using 4 examples as described in the text (large numbers 1 to 4).*

grid area), the value of M^2 on line M^2 is used instead of M on line M (example 2).

If the length is greater than 15 cm, use half of the value of line L and divide the resultant volume by 2 (example 3).

For left ventricular volumes over 300 ml use half of the value of lines L and A and double the resultant volume (example 4).

Examples

(1) L = 10 cm, M = 1·8, A = 60 cm², V = 52·3 (by calculation) and 52·5 (by nomogram). V_{corr} = 44·3.

(2) L = 12 cm, M^2 = 4, A = 160 cm², V = 226 ml (by calculation) and 225 ml (by nomogram). V_{corr} = 184·2.

(3) L = 20 cm, M = 2, A = 60 cm².
V is found to be 37·5 ml from the nomogram using L = 10 cm, M = 2, A = 60. Hence the computed volume when L = 20 cm is 37·5/2 or 18·8 ml. V_{corr} = 17·1.

(4) L = 24 cm, M = 2, A = 280 cm².
V is found to be 172 ml from the nomogram using L = 12, A = 140, M = 2. Hence the volume when L = 24, A = 280, M = 2, is 172 × 2 or 344 ml. V_{corr} = 280·5.

References

Dodge, H. T. (1971). Determination of left ventricular volume and mass. *Radiologic Clinics of North America*, **9,** 459–467.

Dodge, H. T., Sandler, H., Ballew, D. W., and Lord, J. D. (1960). The use of biplane angiocardiography for the measurement of left ventricular volume in man. *American Heart Journal*, **60,** 762–776.

Kasser, I. S., and Kennedy, J. W. (1969). Measurement of left ventricular volumes in man by single plane cineangiocardiography. *Investigative Radiology*, **4,** 83–90.

Kennedy, J. W., Trenholme, S. E., and Kasser, I. S. (1970). Left ventricular volume and mass from single-plane cineangiocardiogram. A comparison of anteroposterior and right anterior oblique methods. *American Heart Journal*, **80,** 343–352.

Snow, J. A., Baker, L. D., Leshin, S. J., and Messer, J. V. (1969). Validation of the single plane cineangiographic determination of canine left ventricular volume. II. Left ventricular dilatation. *Federation Proceedings*, **28,** 517.

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Case reports

British Heart Journal, 1977, **39**, 1147–1149

Fistula from coronary arteries to left ventricle after myocardial infarction[1]

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Coronary arteriography and left ventriculography, performed in a 42-year-old patient with unstable angina seven months after a myocardial infarct showed communications from both the left anterior descending and right coronary arteries to the left ventricular chamber. The area of communication corresponded to the site of infarction as established by electrocardiogram and left ventriculogram. Whether this is a congenital or acquired lesion is unclear.

Although there are many reports of congenital fistulae of the coronary arteries, congenital fistula to the left side of the heart appears to be a rare phenomenon (Hallman *et al.*, 1966; McNamara and Gross, 1969; de Nef *et al.*, 1971; Ogden and Stansel, 1972). We report here a patient who had a fistula, possibly acquired, from both left anterior descending and distal posterior descending coronary arteries to the left ventricle through the site of an old myocardial infarction.

Case history

The patient, a 42-year-old black man, was referred for investigation of exertional chest pain of 22 years' duration. He had noticed the gradual onset of mild chest pain with severe exertion; investigation at that time showed him to be a mild diabetic. An electrocardiogram was reported as within normal limits.

In July 1972 he was admitted to hospital for 2 months because of a prolonged episode of intermittent chest pain at rest associated with T-wave changes on the electrocardiogram. An exercise test in August 1973 showed 4 mm of junctional upsloping ST depression at one minute of stage II of the Bruce graded treadmill test (heart rate of 145 per minute). Three days later, he suffered an acute myocardial infarct of the inferior wall with classic evolution of electrocardiographic findings and serum enzymes. Complete heart block, requiring a temporary pacemaker, occurred on admission to the coronary care unit.

The patient's chest pain continued after discharge, and in November 1973 he began to have nocturnal angina and symptoms of mild paroxysmal nocturnal dyspnoea.

Physical examination revealed a moderately obese man with blood pressure of 125/80 mmHg. He was taking frusemide, 40 mg daily, and spironolactone 100 mg daily. There was no evidence of congestive heart failure. A loud S_4 sound was present but no murmurs were heard. Peripheral pulses were absent bilaterally distal to the popliteal pulses. His electrocardiogram showed signs of old inferior myocardial infarction with a PR interval of 0·18 s (Fig. 1). Chest *x*-ray examination showed a cardiac silhouette at the upper limits of normal size and no evidence of congestive heart failure. Risk factors included smoking, previous hypertension, diabetes, obesity, type IV hyperlipidaemia, and a strong family history of early death from coronary artery disease.

Cardiac catheterisation was performed in March 1974. Left ventriculography revealed an area of decreased motion of the inferior wall corresponding to the old infarction. Ejection fraction was 36 per cent. The left ventricular end-diastolic pressure was 6 mmHg after angiocardiography. The right coronary artery was completely occluded distally, with reconstitution by collaterals from the marginal

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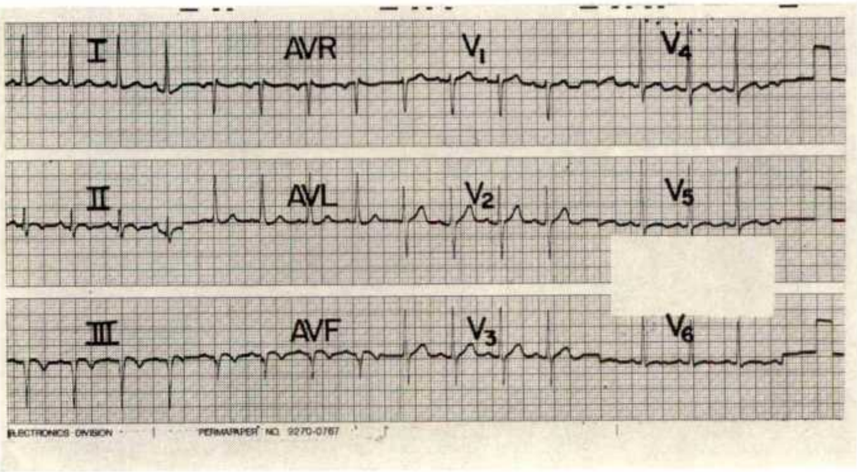

Fig. 1 *Electrocardiogram before coronary angiography in March 1974. Old myocardial infarction of the inferior wall is evident.*

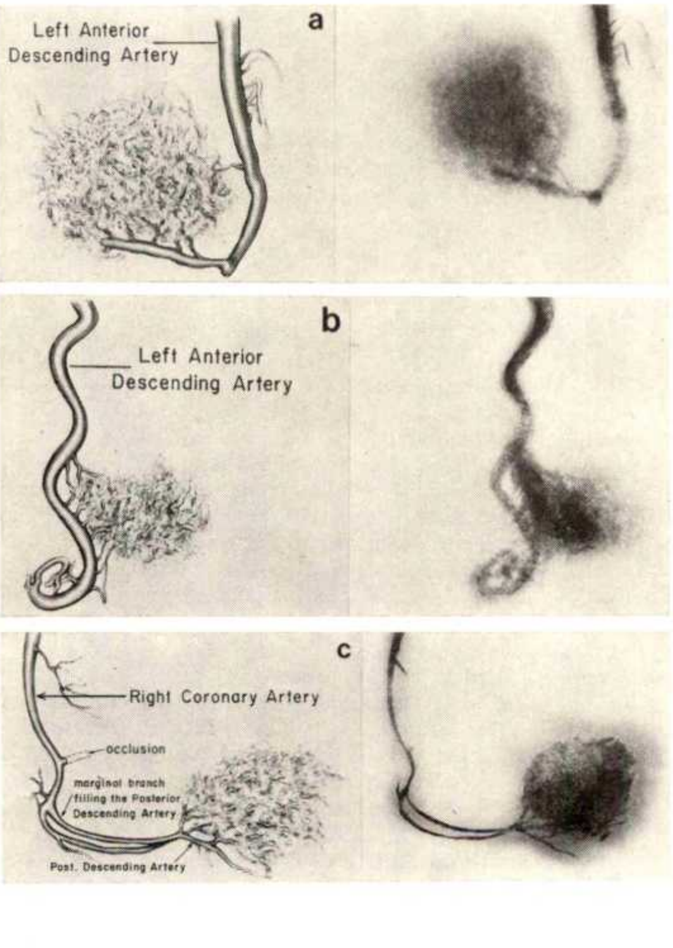
a
Left Anterior Descending Artery
b
Left Anterior Descending Artery
c
Right Coronary Artery
occlusion
marginal branch filling the Posterior Descending Artery
Post. Descending Artery

Fig. 2 *Selective coronary angiography. (a) Distal left anterior descending coronary artery in the 30° right anterior oblique position showing arteriosystemic communication. (b) Distal left anterior descending artery in the 30° left anterior oblique position showing tortuosity of the vessel proximal to the communication. (c) Right coronary artery in the 30° right anterior oblique position showing opacification of the arteriosystemic communication.*

branch. There were diffuse minor irregularities of the proximal right and posterior descending arteries. At the distal end of the latter, there was a localised triangular blush, with rapid passage of dye into the left ventricular chamber.

Injection of the left coronary artery showed no lesion in the main stem; the dilated, tortuous left anterior descending artery emptied very rapidly into a localised diffuse network of vessels which, in turn, emptied into the left ventricle (Fig. 2a and b). A portion of the fistula seen after injection of the left coronary artery was the same as that seen from the right coronary artery (Fig. 2c). The entire fistula filled only from the left coronary artery. The circumflex artery was normal and not dominant. The area of the fistula was faintly calcified.

Discussion

Angina as a manifestation of fistula of the coronary artery is by no means uncommon in adults (Eie and Hillestad, 1971). Fistulae rarely communicate with the left side of the heart and when they do the atrium is usually involved (Effler *et al.*, 1967). It is rarer still for a fistula to drain from both right and left coronary systems. Okuda *et al.* (1973) published the sixth reported case of fistula from the right coronary artery to the left ventricle in March 1973. Reddy *et al.* (1974) reported on a 58-year-old man with a fistula draining all three vessels into the left ventricle. The site of the fistula in their case corresponds exactly to the patient presented here, but that patient had no evidence of previous myocardial infarction.

A coronary artery 'steal syndrome', usually associated with left-to-right shunt, can sometimes be responsible for the symptoms associated with an arteriosystemic communication. Though the steal syndrome could give rise to ischaemia and even to infarction, it is unlikely that our patient had coronary steal alone. Three possibilities exist: (a) the patient had coexistent congenital fistula and coronary disease, (b) the patient had a congenital anomaly of his distal and left coronary arteries with a fistula, or (c) the right ventricular communication evolved from infarction of the inferoapical portion of his septum with extensive collateralisation and re-opening of the thebesian veins. The last of these alternatives was suggested earlier by Phillips and Libanoff (1974).

Several features of our case might favour this last explanation. The patient had many risk factors for coronary artery disease. There were no physical signs of a fistula (no murmurs and diastolic pressure was normal). The right coronary artery was stenosed, and the collateral vessel filling the fistula was not dilated. It is possible that the fistula arose from the infarction of the inferior wall, with collaterals developing early from the left anterior descending artery and later from the right coronary artery.

There are several reports of surgical correction of single-vessel fistulae to the left ventricle (Upshaw, 1962; Sakakibara *et al.*, 1966; Effler *et al.*, 1967; Reddy *et al.*, 1974). Most reports concern correction of left-to-right shunt to prevent the consequences of haemodynamic overload, bacterial endocarditis, and steal syndrome. There is no mention in the published reports of surgical correction of a lesion similar to that described in this patient. It would, indeed, be most difficult to approach, and the results of proximal ligation of either artery to the fistula would be speculative to say the least. We, therefore, elected to treat this patient medically.

References

de Nef, J. J. E., Varghese, P. J., and Losekoot, G. (1971). Congenital coronary artery fistula: analysis of 17 cases. *British Heart Journal*, **33**, 857–862.

Effler, D. B., Sheldon, W. C., Turner, J. J., and Groves, L. K. (1967). Coronary arteriovenous fistulas: diagnosis and surgical management. Report of 15 cases. *Surgery*, **61**, 41–50.

Eie, H., and Hillestad, L. (1971). Arterio-venous fistulae of the coronary arteries: a report of six cases. *Scandanavian Journal of Thoracic and Cardiovascular Surgery*, **5**, 34–38.

Hallman, G. L., Cooley, D. A., and Singer, D. B. (1966). Congenital anomalies of the coronary arteries: anatomy, pathological, and surgical treatment. *Surgery*, **59**, 133–144.

McNamara, J. J., and Gross, R. E. (1969). Congenital coronary artery fistula. *Surgery*, **65**, 59–69.

Ogden, J. A., and Stansel, H. C., Jr. (1972). Coronary arterial fistulas terminating in the coronary venous system. *Journal of Thoracic and Cardiovascular Surgery*, **63**, 172–182.

Okuda, Y., Tsuneda, T., Morishima, A., Matsumoto, S., Ito, Y., and Tsuzuki (1973). Right coronary artery to left ventricle fistula; the sixth case in the literature and discussion. *Japanese Heart Journal*, **14**, 184–191.

Phillips, P. A., and Libanoff, A. J. (1974). Arteriovenous communication associated with obstructive arteriosclerotic coronary artery disease and myocardial infarction. *Chest*, **65**, 106–108.

Reddy, K., Gupta, M., and Hamby, R. I. (1974). Multiple coronary arteriosystemic fistulas. *American Journal of Cardiology*, **33**, 304–306.

Sakakibara, S., Yokoyama, M., Takao, A. Nogi, M., and Gomi, H. (1966). Coronary arteriovenous fistula: nine operated cases. *American Heart Journal*, **72**, 307–314.

Upshaw, C. B., Jr. (1962). Congenital coronary arteriovenous fistula. Report of a case with an analysis of 73 reported cases. *American Heart Journal*, **63**, 399–404.

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British Heart Journal, 1977, **39**, 1150–1153

Varicella myocarditis presenting with unusual ventricular arrhythmias

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A 10-year-old boy with varicella developed syncopal episodes caused by runs of self-terminating ventricular tachycardia and ventricular fibrillation. These arrhythmias were thought to be caused by varicella myocarditis and were resistant to most common antiarrhythmic agents. Continuous electrocardiographic recording and analysis proved extremely useful in the management of this case. Mexiletine, a new antiarrhythmic drug, was finally effective in controlling recurrent attacks of ventricular tachycardia.

At least 18 viruses are known to affect the heart (Abelmann, 1971). The varicella-zoster virus is one of the most rare. Since the necropsy findings in varicella myocarditis were first described by Hackel (1953), several reports have appeared (Cheatham *et al.*, 1956; Tatter *et al.*, 1964; Morales *et al.*, 1971) mainly concerned with histological changes in cardiac muscle. Recovery from varicella myocarditis has been reported in only 3 patients (De Medeiros Neto *et al.*, 1961; Moore *et al.*, 1969).

This report describes a child who presented with syncopal episodes caused by self-terminating ventricular arrhythmias during the course of clinical varicella. These arrhythmias, in the absence of other recognisable precipitating factors, were thought to be the result of myocarditis occurring as a complication of varicella.

Case report

A healthy 10-year-old boy became ill after contact with his grandfather who had herpes zoster 2 weeks previously. He developed a mild fever followed by a papulo-vesicular eruption on his trunk and face. A diagnosis of varicella was made. Five days later his condition deteriorated and he developed vomiting and headache. At this stage he had 2 syncopal episodes lasting approximately 3 to 4 minutes each. These were associated with eye rolling and convulsive movements of his limbs. There was no incontinence or postictal headache and weakness. His general practitioner referred him to hospital with a tentative diagnosis of varicella encephalitis.

His previous medical history was unremarkable except for a febrile convulsion at the age of 3 during an attack of measles.

On admission he was fully conscious, alert, and apyrexial. On his trunk there were fading varicella lesions. His pulse was noted to be irregular, with a rate of 50 to 60 beats per minute. No other abnormal findings were detected in the cardiorespiratory or alimentary systems. Central nervous system examination was normal. A lumbar puncture was performed and showed no increase in cells and a normal protein and sugar content. A further syncopal episode occurred 12 hours after admission. His chest *x*-ray film, full blood count, and electroencephalogram were normal. An electrocardiogram, however, showed a basic sinus bradycardia with frequent multiform ventricular ectopic beats and short bursts of ventricular tachycardia.

Bedside electrocardiographic monitoring and continuous electrocardiographic tape recordings were instituted and these showed that the syncopal episodes were the result of self-terminating runs of ventricular fibrillation (Fig. 1).

Intravenous lignocaine was started but over the following 48 hours several further episodes of ventricular fibrillation occurred, some lasting 1 to 1½ minutes. Lignocaine, procainamide, and phenytoin proved ineffective in controlling the arrhythmia and he was subsequently transferred to a coronary care unit. Continuous electrocardiographic tape recordings were made for the next 8 weeks. The tapes were processed using a Neilson arrhythmia computer and were also visually analysed. This provided a total ventricular ectopic beat count and a continuous graph of ventricular ectopic beat activity for each 24 hours, thus allowing accurate assessment of the effectiveness of further treatment. Surveillance was maintained during a period of mobility with an Oxford Instruments Miniature analogue tape recorder.

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On transfer to the coronary care unit treatment

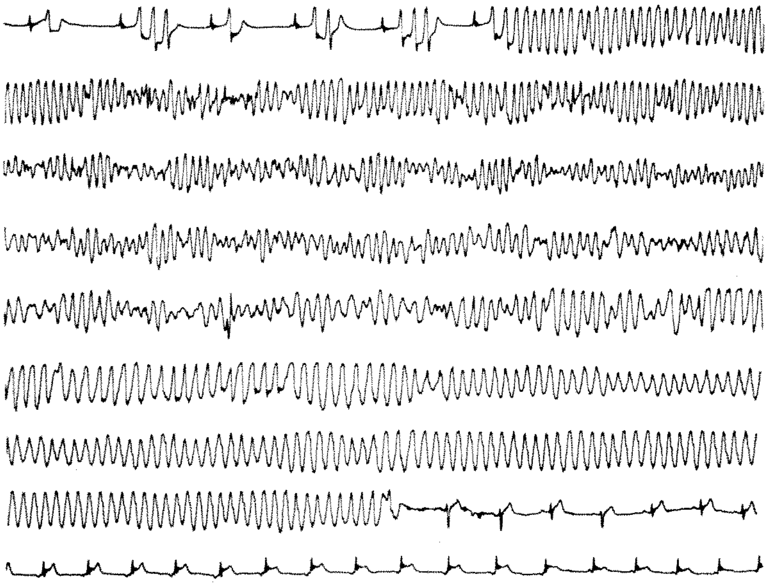

Fig. 1 *A write-out from the continuous electrocardiographic tape recording illustrates ventricular tachycardia degenerating into ventricular fibrillation. Return to sinus rhythm occurred spontaneously.*

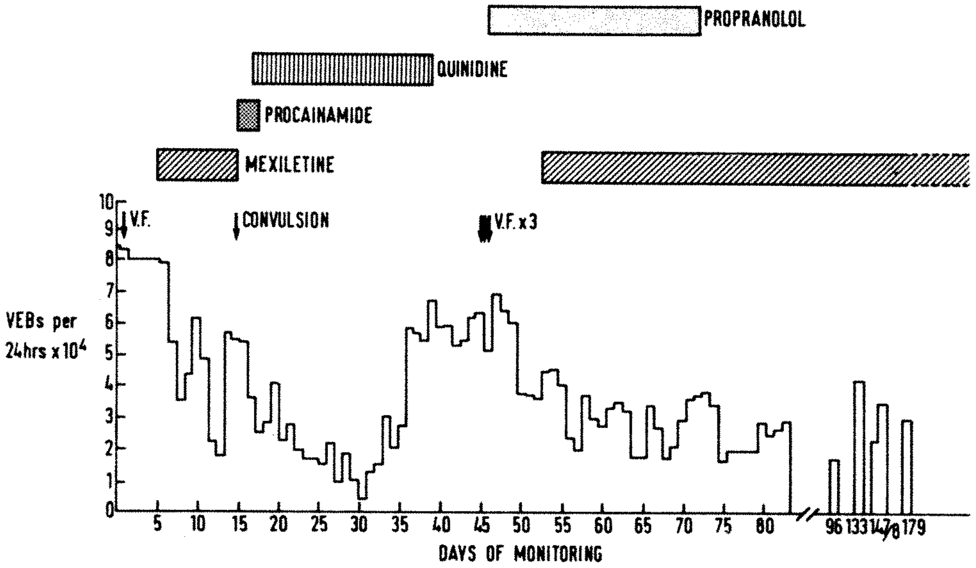

Fig. 2 *Histogram of the total ventricular ectopic beat count over the period of observation and treatment. The ventricular ectopic beat count was charted on a daily basis, and the variation in the pattern of the ectopic count in relation to the different treatment schedules is shown. Out-patient ectopic beat counts between the 96th day and the 179th day are shown on the right.*

was started with mexiletine, a new oral antiarrhythmic agent structurally similar to lignocaine, which has proved effective in ventricular arrhythmias associated with myocardial infarction (Campbell *et al.*, 1975). On a dosage regimen which produced a drug serum concentration at the upper limit of the therapeutic range there was a brief self-terminating convulsive episode not associated with any cardiac arrhythmia. After this mexiletine was discontinued and quinidine started in a dosage of 200 mg 6 hourly; this induced an 'L-E syndrome' with fever, lymphadenopathy, hepatosplenomegaly, and a weakly positive antinuclear factor. When this was withdrawn 3 episodes of ventricular fibrillation occurred requiring DC cardioversion. Propranolol was then started without effect on ectopic beat activity. At this time echocardiography, cardiac catheterisation, and angiography were performed and all were within normal limits, apart from reduced contractility of both ventricles which could have been related to the propranolol administration. Atrial pacing at 120 beats per minute abolished the ventricular actopic activity. An endomyocardial biopsy specimen proved too traumatised for histological examination. He was restarted on mexiletine and the propranolol was continued for a further 3 weeks. Serological evidence of varicella infection was obtained 8 weeks after admission with a titre of 1:128. Fig. 2 illustrates the total ventricular ectopic count over the period of observation, charted on a daily basis along with the various treatment schedules. In general, lower total ventricular ectopic counts were associated with fewer episodes of ventricular tachycardia. The ectopic activity eventually settled and became stable on mexiletine in a dosage of 450 mg daily.

He was discharged home on mexiletine 12 weeks after admission, having been free of syncopal episodes for 6 weeks. He remains well at follow-up with stabilisation of ectopic activity as shown by 24-hour electrocardiograms taken at out-patient visits up to 6 months after his illness.

Discussion

The true incidence of myocardial involvement in the common viral illnesses of childhood is difficult to assess. The majority of cases are subclinical or are found to have minor 'T' wave changes on the electrocardiogram (*Lancet*, 1974). Recently myalgia has been reported as being an important diagnostic clue to the presence of myocarditis in viral illness (Lewes *et al.*, 1974) but was absent in this case.

Previous reports of varicella myocarditis have mainly concerned cases of fulminating infection with multiorgan involvement (Hackel, 1953; Tatter *et al.*, 1964; Morales *et al.*, 1971). This case, however, did not show severe infection, and apart from the arrhythmias was associated with a normal clinical course. Documented arrhythmias in varicella myocarditis have been supraventricular in origin (De Medeiros Neto *et al.*, 1961; Tatter *et al.*, 1964; Moore *et al.*, 1969) and resulted in congestive cardiac failure. One report of sudden death in varicella myocarditis showed viral involvement of the conducting tissue at necropsy (Morales *et al.*, 1971). Neither supraventricular arrhythmias nor conduction disturbances were noted in this case. This report, to our knowledge, is the only case of varicella myocarditis recorded in which ventricular arrhythmias have been documented, and suggests a possible mechanism of sudden death in patients with myocardial involvement during the course of a viral illness.

The ventricular arrhythmias recorded in this case were of interest as similarly appearing ventricular arrhythmias known as *'torsade de pointes'* ('wave bursts') have been described (Dessertenne, 1966; Motte *et al.*, 1970; Brochier *et al.*, 1972) in which the basic sinus rate is slow with a long QT interval and is interrupted by frequent bursts of bizarrely appearing ventricular tachycardia with altering waveform. The bursts of tachycardia begin with a 'R on T' ventricular ectopic beat and are usually self-terminating but can degenerate into fatal ventricular fibrillation. These arrhythmias have been described in association with chronic atrioventricular block, quinidine, and chlorpromazine toxicity, the long QT interval syndromes, myocardial ischaemia, magnesium deficiency, potassium depletion (Brochier *et al.*, 1972), and excessive sodium bicarbonate ingestion (Caponnetto *et al.*, 1974). As in this patient the arrhythmias have been difficult to treat and have been resistant to the commonly used antiarrhythmic agents, responding only to rapid pacing. Myocarditis has not previously been reported to produce the *'torsade de pointes'* arrhythmia. Impairment of sinoatrial node function attributable to the myocarditis may have produced the sinus bradycardia in this patient. This rhythm in the setting of an already irritable myocardium with frequent ectopic activity almost certainly allowed the development of *'torsade de pointes'*. The gradual reduction in ectopic activity may have been the result of a spontaneous improvement resulting from the natural history of the illness and/or more adequate administration of mexiletine as reflected in serum levels which were more consistently within a therapeutic range.

We are grateful to Dr. George Sangster for referring this case.

References

Abelmann, W. (1971). Virus and the heart. *Circulation,* **44,** 950–956.

Brochier, M., Motté, G., and Fauchier, J. P. (1972). Tachycardie ventriculaire en torsades de pointe. *Actualités Cardio-Vasculaires Médico-Chirurgicales,* **6,** 171–177.

Campbell, R. W. F., Talbot, R. G., Dolder, M. A., Murray, A., Prescott, L. F., and Julian, D. G. (1975). Comparison of procainamide and mexiletine in prevention of ventricular arrhythmias after acute myocardial infarction. *Lancet,* **1,** 1257–1259.

Caponnetto, S., Pastorini, C., and Masperone, M. A. (1974). Crisi di fibrillazione ventricolare a 'torsione di punta' per introduzione di cospicua quantita' di bicarbonato di sodio. *Giornale Italiano di Cardiologia,* **4,** 211–216.

Cheatham, W. J., Weller, T. H., Dolan, T. F., and Dower, J. C. (1956). Varicella: report of two fatal cases with necropsy, virus isolation and serologic studies. *American Journal of Pathology,* **32,** 1015–1028.

De Medeiros Neto, G. A., De Almeida, D. B., and Facchini, F. P. (1961). Miocardite em associacão com varicela. *Revista do Hospital das Clinicas de Faculdade de Medicina da Universidade de Sao Paulo,* **16,** 427–430.

Dessertenne, F. (1966). La tachycardie ventriculaire à deux foyers opposés variables. *Archives des Maladies du Coeur et des Vaisseaux,* **59,** 263–272.

Hackel, D. B. (1953). Myocarditis in association with varicella *American Journal of Pathology,* **29,** 369–379.

Lancet (1974). Viruses and heart disease. **2,** 991.

Lewes, D., Rainford, D. J., and Lane, W. F. (1974). Symptomless myocarditis and myalgia in viral and *myocoplasma pneumoniae* infections. *British Heart Journal,* **36,** 924–932.

Moore, C. M., Henry, J., Benzing, G., and Kaplan, S. (1969). Varicella myocarditis. *American Journal of Diseases of Children,* **118,** 899–902.

Morales, A. R., Adelman, S., and Fine, G. (1971). Varicella myocarditis: a case of sudden death. *Archives of Pathology,* **91,** 29–31.

Motte, G., Coumel, P. N., Abitbol, G., Dessertenne, F., and Slama, R. (1970). Le syndrome QT long et syncopes par 'torsades de pointe'. *Archives des Maladies du Coeur et des Vaisseaux,* **63,** 831–853.

Tatter, D., Gerard, P. W., Silverman, A. H., Wang, C., and Pearson, H. E. (1964). Fatal varicella pancarditis in a child. *American Journal of Diseases of Children,* **108,** 88–93.

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Left atrial metastasis of chorion carcinoma, presenting as mitral stenosis

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A 35-year-old woman developed symptoms of multiple system disease. Three months later she was admitted to hospital and died six days after admission, with signs suggestive of mitral stenosis. Postmortem examination indicated primary chorion carcinoma of the right ovary with metastases to the left atrium, lungs, brain, kidneys, pancreas, mesenteric arteries, and spleen. The signs and symptoms, and the morphological and histological findings at necropsy, are discussed.

History

In February 1975, a 35-year-old mother of two children developed severe left-sided chest pain, headache, transient paraesthesiae, and pareses of the upper extremities, visual disturbance, agnosia, motor aphasia, and abdominal symptoms. She was admitted to our hospital three months later because of unclear pulmonary symptoms and recurrent tachycardia. The obstetric history was unremarkable.

CLINICAL AND LABORATORY FINDINGS

On clinical examination the patient was febrile and appeared chronically ill but was not in acute distress. She was slightly dyspnoeic and had a tachycardia varying between 100 and 160 beats/min. The cardiac findings were consistent with mitral stenosis. The blood pressure ranged between 140/90 and 170/110 mmHg. Slight paresis of the right arm and increased right-sided tendon reflexes were noticed. Gynaecological examination revealed some tenderness of the recto-vaginal pouch but the examination was otherwise unremarkable. The electrocardiogram showed sinus tachycardia, left atrial hypertrophy, and evidence of right and left ventricular hypertrophy. The phonocardiogram showed the typical signs of mitral stenosis: accentuated first heart sound, mitral opening snap, low frequency protodiastolic murmur, and discrete presystolic murmur. The chest *x*-ray showed a typical 'mitralised configuration' of the heart, with evidence of an enlarged left atrium, filling out of the left-sided waist of the heart, a prominent pulmonary conus, and ill-defined and somewhat irregular margins of the hilar shadows, as well as various small patchy densities in both upper lung regions. An echocardiographic examination was not performed.

Pathological laboratory data consisted of a raised ESR of 69/95 mm, a leucocytosis of $10{\cdot}5 \times 10^9/l$, and a pronounced anaemia with a haemoglobin of 9 g/dl.

DIAGNOSIS AND COURSE

The following diagnoses were considered: (1) bacterial endocarditis complicating mitral stenosis; (2) left-sided atrial myxoma with multiple systemic embolism; (3) collagen disorders such as systemic lupus erythematosus or polyarteritis nodosa in addition to mitral stenosis; and (4) advanced metastatic tumour disease. The patient's condition deteriorated rapidly so that it was impossible to perform further diagnostic procedures such as cardiac catheterisation and angiocardiography. Despite treatment with digitalis and diuretics pulmonary congestion increased and neurological symptoms progressed; the patient died six days after admission to hospital.

PATHOLOGY AND HISTOLOGY

A primary chorion carcinoma of the right ovary with multiple metastases was found on necropsy. Histological examination of serial sections of the uterus failed to show a tumour lesion in this organ. The most impressive finding was a metastasis in the left atrium measuring $4{\cdot}0 \times 2{\cdot}5 \times 3{\cdot}5$ cm, which caused a high grade stenosis of the mitral orifice (Fig.), with backward extension into the pulmonary veins of the left upper lobe as far as the first branch-

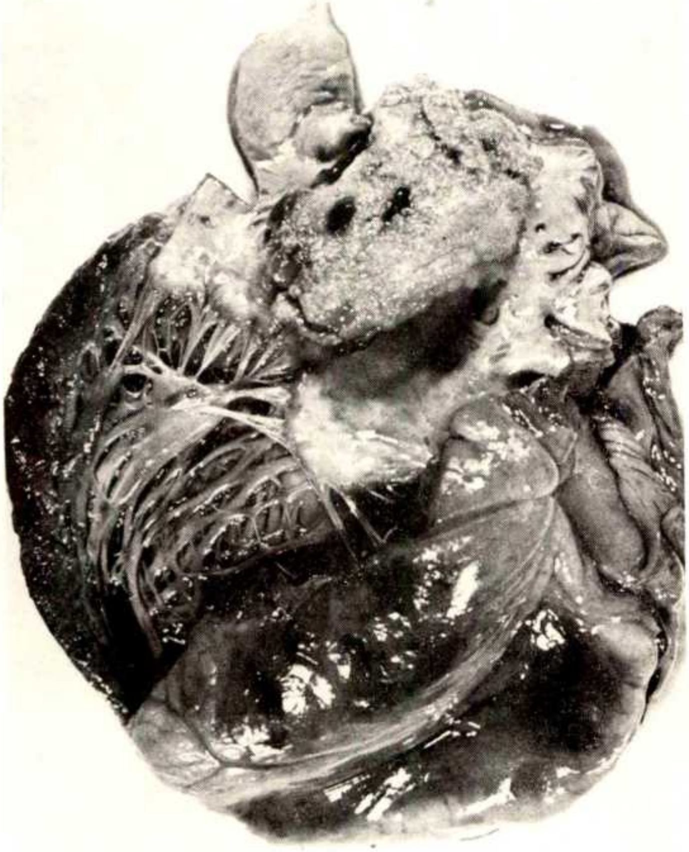

Fig. *Metastatic tumour mass in the left atrium causing severe obstruction of the mitral orifice.*

ing. Tumour tissue was also detected in the spleen, intestinal tract, kidneys, pancreas, brain, and pulmonary lymphatics.

Comment

Cardiac tumours are rare. In unselected necropsies primary cardiac tumours are found in 0·05 per cent, and metastatic cardiac tumours in 0·6 to 6·4 per cent; in cases with malignant tumours, however, cardiac metastases are found in up to 21 per cent (Griffiths, 1965; Berge and Sievers, 1968; Friedberg, 1972). In principle, any metastasising tumour may also produce cardiac metastases. Carcinomata of the bronchial tree and the breast and malignant lymphoma tend to metastasise to the heart in 23 to 33 per cent (Hanfling, 1960; Roberts *et al.,* 1968). In malignant melanoma metastases to the heart occur in up to 50 per cent of cases (Glancy and Roberts, 1968). Only 10 per cent of cardiac metastases cause cardiac symptoms (Hurst, 1974). Site, size, and tendency to embolism determine the clinical findings; metastases to the heart may mimic valvular disease, or produce electrocardiographic features of myocardial infarction and conduction defects (James, 1962; Conde *et al.,* 1975). When sinus rhythm is present, multiple systemic embolism should always suggest the possibility of a cardiac tumour, particularly of left atrial myxoma (Goodwin, 1963; Greenwood, 1968). Atrial tumours presenting as mitral stenosis are most commonly myxomata, occasionally pedunculated sarcoma, and very rarely metastases (Sterns *et al.,* 1966; Friedberg 1972).

There is a high incidence of local metastases in chorion carcinoma, and less frequently metastases are found in lungs, liver, and brain, rarely in kidneys, spleen, and heart. If the chorion carcinoma causes cardiac metastases at all, they are usually to the right side of the heart (*Handbuch*, 1930).

A metastasis of chorion carcinoma to the left atrium has not been described so far to our knowledge and, therefore, must be regarded as a rarity.

In the case described above the clinical features were primarily suggestive of a generalised inflammatory disease. The absence of a rheumatic history, the rapid progression of the cardiac symptoms, and the variation of the A_2-OS interval in association with multiple systemic embolism favoured the diagnosis of an atrial tumour. A metastatic cardiac tumour seemed unlikely, since there was no clinical evidence of a primary tumour.

Lymphatics and veins function as pathways for the metastasising chorion carcinoma (Hanfling 1960; Rogen and Moffat, 1967). Apparently, the left atrial metastasis was initially attached to the atrial endocardium after having passed the pulmonary circulation, and extended from there backwards into the pulmonary veins. The systemic tumour emboli obviously originated from the left atrial metastasis.

References

Berge, T., and Sievers, J. (1968). Myocardial metastases. A pathological and electrocardiographic study. *British Heart Journal,* **30,** 383–390.

Conde, C. A., Meller, J., Pantazopoulos, J., Donoso, E., and Dack, S. (1975). Reticulum-cell sarcoma with intracardiac metastases. *American Journal of Cardiology,* **36,** 357–361.

Friedberg, C. K. (1972). *Erkrankungen des Herzens.* Georg Thieme, Stuttgart.

Glancy, D. L., and Roberts, W. C. (1968). The heart in malignant melanoma: a study of 70 autopsy cases. *American Journal of Cardiology,* **21,** 555–571.

Goodwin, J. F. (1963). Diagnosis of left atrial myxoma. *Lancet,* **1,** 464–468.

Greenwood, W. F. (1968). Profile of atrial myxoma. *American Journal of Cardiology,* **21,** 367–375.

Griffiths, G. C. (1965). A review of primary tumors of the heart. *Progress in Cardiovascular Diseases,* **7,** 465–479.

Handbuch der speziellen pathologischen Anatomie (1930). Vol. 7, Part I, pp. 713–801. Springer, Berlin.

Hanfling, S. M. (1960). Metastatic cancer to the heart: review of the literature and report of 127 cases. *Circulation,* **22,** 474–483.

Hurst, J. W. (1974). *The Heart,* 3rd ed. McGraw-Hill, New York.

James, T. N. (1962). Metastasis of hypernephroma to atrioventricular node: report of a case. *New England Journal of Medicine,* **266,** 705–708.

Roberts, W. C., Glancy, D. L., and DeVita, V. T., Jr. (1968). Heart in malignant lymphoma (Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma and mycosis fungoides): a study of 196 autopsy cases. *American Journal of Cardiology,* **22,** 85–107.

Rogen, A. S., and Moffat, A. D. (1967). Unusual secondary tumour of heart. *British Heart Journal,* **29,** 638–640.

Sterns, L. P., Eliot, R. S., Varco, R. L., and Edwards, J. E. (1966). Intracavitary cardiac neoplasms. A review of fifteen cases. *British Heart Journal,* **28,** 75–83.

Requests for reprints to Dr. Alois Hepp, Medizinische Universitätsklinik, Otfried-Müller-Strasse, 74 Tübingen, West Germany.

British Heart Journal, 1977, **39**, 1157–1158

Recurrent migraine after propranolol

R. H. ROBSON

From the University Department of Therapeutics, The Royal Infirmary, Edinburgh

A 70-year-old woman with angina pectoris developed a migrainous headache 3 days after starting oral propranolol. She had not complained of headaches since her second and third decade when she had suffered occasional attacks of migraine. It is likely that propranolol was the cause of her headache, since it recurred when she was rechallenged with the drug.

Propranolol has been used in the treatment of migraine (Børgesen *et al.*, 1974; Widerøe and Vigander, 1974; *Drug and Therapeutics Bulletin*, 1975), though the mode of action has not been elucidated. However, in the case reported here, propranolol appeared to precipitate vascular headaches. The patient was subsequently challenged with propranolol and placebo.

Case report

A 70-year-old woman with a 20-year history of angina pectoris was admitted to hospital with severe persistent chest pain, occurring at rest, suggestive of myocardial ischaemia. A similar attack had occurred two months previously, but had been treated at home. She took nitroglycerin regularly in addition to thyroid replacement therapy for hypothyroidism. Although she had suffered from migraine (consisting of headache, visual disturbances, and vomiting) in her second and third decade, she had had no headaches for many years. Examination showed no abnormalities. The heart rate was 76/minute and the blood pressure was 130/70.

Investigations revealed normal haemoglobin, blood urea and electrolytes, liver function tests, serum levels of cardiac enzymes and thyroxine, and a normal chest *x*-ray film. Serial electrocardiograms were normal.

A diagnosis of coronary insufficiency was made and treatment consisted of bed rest and propranolol 40 mg t.d.s. She had no further chest pain after admission, but on the third and fourth days of treatment, she suffered from severe bilateral, frontal headaches, associated with teichopsia, photophobia, and difficulty in focusing, but no nausea or vomiting. The propranolol was stopped, and the headaches resolved within 8 hours of the last dose.

She was discharged and remained well, apart from stable angina, requiring regular nitroglycerin; she had no further headaches.

Five months after discharge, the patient was rechallenged double-blind with propranolol and placebo, the first treatment being one tablet on day 1, one b.i.d. on day 2, and one t.d.s. for the rest of the week, the alternative treatment being similarly administered the following week. In week 1 (placebo), her angina remained stable and no headaches occurred. On day 5 of week 2 (propranolol 40 mg) the patient suffered a severe bilateral, frontal headache, lasting for 12 hours and associated with photophobia but no nausea. The following day she stopped taking the drug and the headache disappeared within 12 hours of the last dose. The trial was terminated in view of the distinct symptomatology.

Discussion

Propranolol appeared to precipitate vascular headaches in this patient, even though it is sometimes used for the prophylaxis of migraine (Børgesen *et al.*, 1974; Widerøe and Vigander, 1974; *Drug and Therapeutics Bulletin*, 1975). In the period 1964 to 1973, there were five reports to the Committee on Safety of Medicines of headache related to propranolol, one related to oxprenolol, and one to practolol, but no reports of migraine. In view of a previous report of two incidents of migraine in patients taking propranolol (Sharpe, 1974), this seems to be a possible side-effect of propranolol, and maybe other β-blockers.

I thank Professor R. H. Girdwood for permission to report this case, and I.C.I. for supplying propranolol and placebo.

References

Børgesen, S. E., Nielsen, J. L., and Møller, C. E. (1974). Prophylactic treatment of migraine with propranolol. *Acta Neurologica Scandinavica,* **50,** 651–656.

Drug and Therapeutics Bulletin (1975). Propranolol for migraine. **13,** 93–96.

Sharpe, C. J. (1974). Propranolol in the treatment of migraine. *British Medical Journal,* **3,** 522.

Widerøe, T.-E., and Vigander, T. (1974). Propranolol in the treatment of migraine. *British Medical Journal,* **2,** 699–701.

Requests for reprints to Dr. R. H. Robson, University Department of Therapeutics, The Royal Infirmary, Edinburgh EH3 9YW.

Correspondence

British Heart Journal, 1977, **39,** 1159–1161

Echocardiographic diagnosis of primitive ventricle with two atrioventricular valves

Sir,

Dr. Beardshaw and colleagues are to be congratulated on a further excellent correlation between anatomy and echocardiography in complex congenital heart disease (*British Heart Journal,* 1977, **39,** 266).

I would like only to sound a soft caveat on two of the conclusions made in the echocardiographic study.

The unusual posterior excursion of the septal leaflet of the anterior atrioventricular valve in primitive ventricle cannot safely be used to differentiate this condition from congenitally corrected transposition. Just such motion may occasionally be recorded in corrected transposition when the echo transducer is positioned low and close to the sternal edge. The septum becomes indistinct and the posterior leaflet of the right-sided mitral valve appears to dip back into the left ventricle (Fig. 1). This may perhaps be explained by the relatively posterior siting of the larger mitral leaflet when this valve is rightsided.

In carrying out a simple valve count in small infants, when a full-scale deflection of 5 or 6 cm is often used in the recorder, care is necessary before interpreting fast-moving echoes as originating from

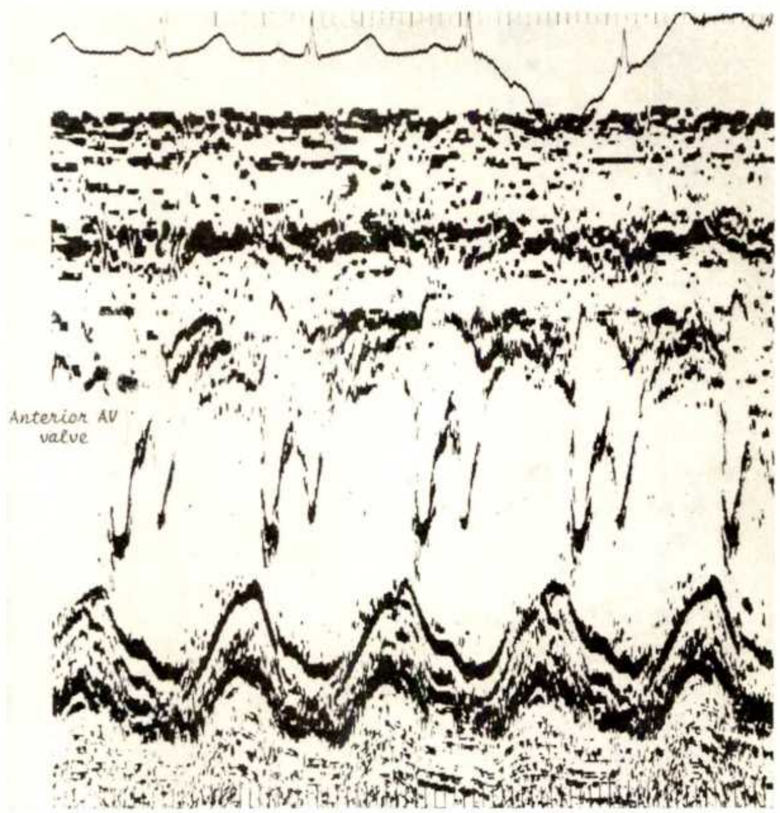

Fig. 1 *Echocardiograms of anterior atrioventricular valve showing unusual posterior excursion of posterior leaflet. Congenitally corrected transposition in a boy of 7 years with no defect of the ventricular septum (angiographic diagnosis).*

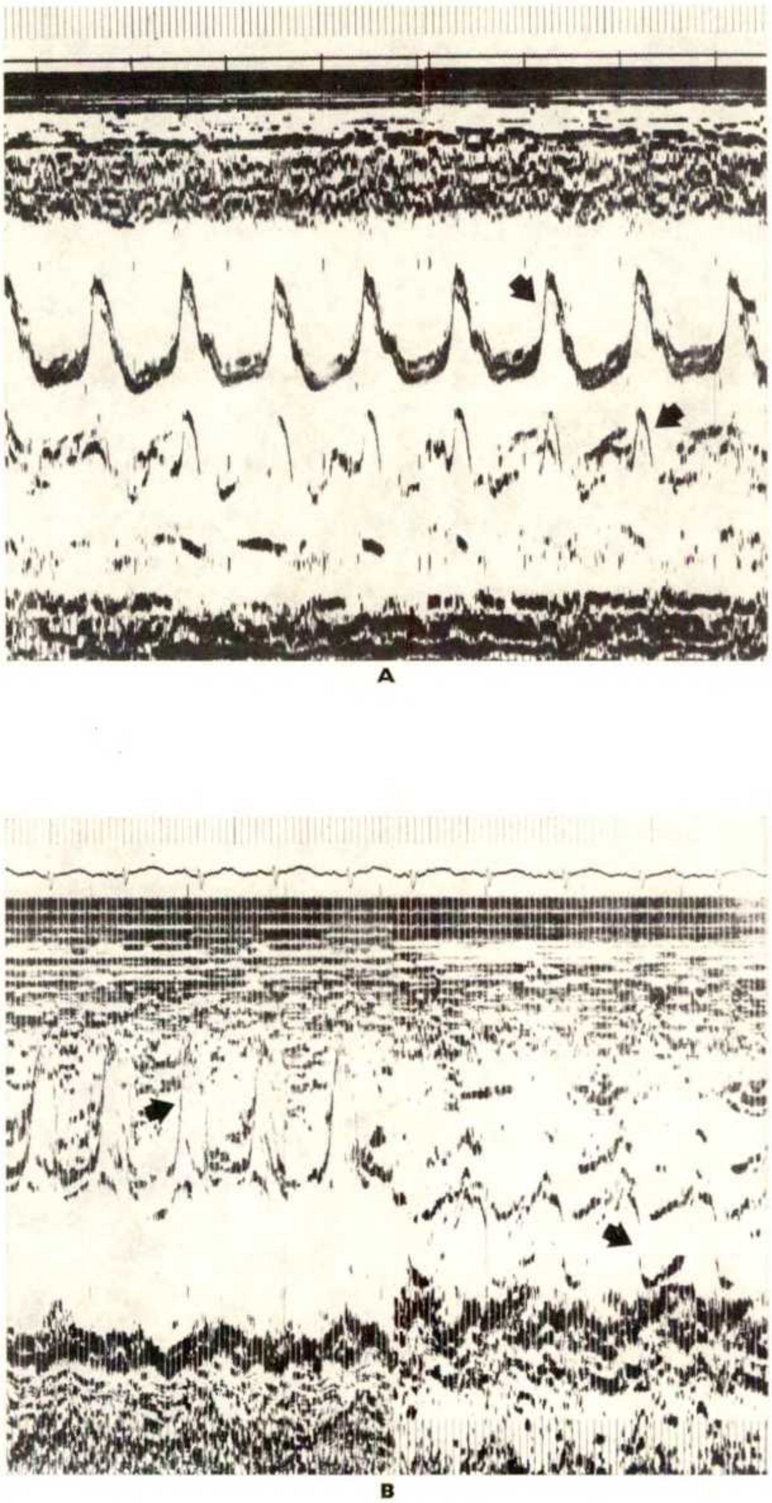

Fig. 2 *Spurious echoes suggestive of a second (posterior) atrioventricular valve where none exists (arrows).* (A) *Infant with single ventricle, mitral atresia and truncus arteriosus (necropsy diagnosis).* (B) *Edited scan in an infant with common atrium, single atrioventricular valve, single ventricle and pulmonary atresia (necropsy diagnosis).*

an atrioventricular valve (I refer particularly to the left atrioventricular valve illustrated by the authors in their Fig. 7).

Similar echoes may be recorded from structures other than atrioventricular valves, giving the appearance of two valves where only one exists (Fig. 2 A and B).

To determine the presence of two atrioventricular valves with any degree of certainty requires the recording of echoes with the classical configuration of atrioventricular valve movement.

J. S. Wright,
Victoria Hospital
Blackpool FY3 8NR

This letter was shown to Dr. Beardshaw and colleagues who reply as follows:

We are most grateful to Dr. Wright for his comments on our paper. He correctly stresses that the diagnosis of primitive ventricle by echocardiography is not straightforward. We were of course aware that unusual posterior excursion of the septal leaflet of the anterior atrioventricular valve could also occur in congenitally corrected transposition, and indeed we have collaborated with Dr. Wright in presenting a paper to the Cardiac Society making this point (Beardshaw *et al.*, 1976). The echo behind the atrioventricular valve in Fig. 2A is of interest and presents an unusual appearance. It certainly shows morphology as near that of the anterior cusp of an atrioventricular valve as one could expect at the heart rate, and raises the possibility that it might have originated from the atretic posterior atrioventricular valve. We also have examples of recordings of this type. Fig. 2B stresses the importance of recording echoes from both atrioventricular valves simultaneously if the diagnosis of primitive ventricle with two atrioventricular valves is to be confirmed.

Yours etc.

Judith A. Beardshaw, Derek G. Gibson,
Michael C. Pearson, Mark T. Upton,
Robert H. Anderson
Departments of Paediatrics, Cardiology
and Radiology
Cardiothoracic Institute
Brompton Hospital
London SW3 6HP

Reference

Beardshaw, J. A., Gibson, D. G., Wright, J. S., Pearson, M. C., and Anderson, R. H. (1976). Echocardiographic diagnosis of corrected transposition (abstract). *British Heart Journal*, **38**, 878.

Correspondence

British Heart Journal, 1977, **39**, 1162

Surgical treatment of postinfarction left ventricular aneurysm in 32 patients

Sir,

We read the paper by Dr. Donaldson and his colleagues on the surgical treatment of postinfarction left ventricular aneurysm with interest (Donaldson *et al.* (1976), **38,** 1223).

The authors state that 'the angiographic criteria for the diagnosis of left ventricular aneurysm are not generally agreed and are unreliable'. This is because of the confusion in pathological nomenclature. While we agree that 'the left ventriculogram is *not* diagnostic' (alone) our experience indicates that the combination of typical coronary angiographic anatomy with a sizeable dyskinetic segment in its territory or supply *is* diagnostic. If the supplying vessel is totally occluded and fails to fill retrogradely (Raphael *et al.,* 1972) the surgeon will find a full thickness fibrous aneurysm bulging the exterior of the heart (Edwards, 1961), resection of which is likely to lead to symptomatic improvement. If the obstructed artery is patent beyond the block and fills retrogradely, or if its obstruction is less than complete then the infarct will not amount to an aneurysm but a transmural fibrous scar. This is not an aneurysm even when 'clearly delineated from the surrounding muscle'. As we do not yet know the prognosis of dyskinesia compared with aneurysm, the distinction should be maintained.

This point is made in Table 2. It shows that patients without total coronary occlusions had only small resections compared with patients who had totally occluded arteries, and clinical improvement in the former group may have resulted from the other procedures that were carried out.

C. M. Oakley and M. J. Raphael,
Royal Postgraduate Medical School,
Hammersmith Hospital, London W12.

References

Edwards, J. E. (1961). *An Atlas of Acquired Diseases of the Heart and Great Vessels,* Vol. II, p. 615. W. B. Saunders, Philadelphia.

Raphael, M. J., Steiner, R. E., Goodwin, J. F., and Oakley C. M. (1972). Cine-angiography of left ventricular aneurysms. *Clinical Radiology,* **23,** 129–139.

This letter was shown to the authors who reply as follows.

Sir,

We are grateful to Dr. Oakley and Dr. Raphael for their observations on our paper. However, in our experience, the demonstration of retrograde filling of a vessel in the territory of a presumed aneurysm does not necessarily mean that the surgeon will not find a resectable aneurysm (by our definition). Our point is that the presence or absence of a resectable fibrous scar or aneurysm cannot be reliably predicted before operation, though the preoperative assessment is commonly correct.

R. Balcon and M. Honey,
London Chest Hospital,
London E2.

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3. Clin. Pharm. Ther., 15, 141, (1974)
4. J. Int. Med. Res., 2, 314, (1974)
5. Brit. J. Clin. Prac., 28, 311, (1974)
6. Brit. J. Clin. Prac., 29, 7, (1975)
7. Postgrad. Med. J., 51, (Suppl. 6), 54, (1975)
8. Brit. J. Clin. Prac. 30, 11-14 (1976)
9. Leading Article, Brit. Med. J., 2, 521, (1975)
10. J. Int. Med. Res., 3, 241, (1975)
11. Postgrad. Med. J., 51, (Suppl. 6), 71, (1975)
12. Acta. Med. Scand., 193, 119, (1973)
13. J. Int. Med. Res., 3, 104, (1975)
14. J. Int. Med. Res., 4, 37-41 (1976)

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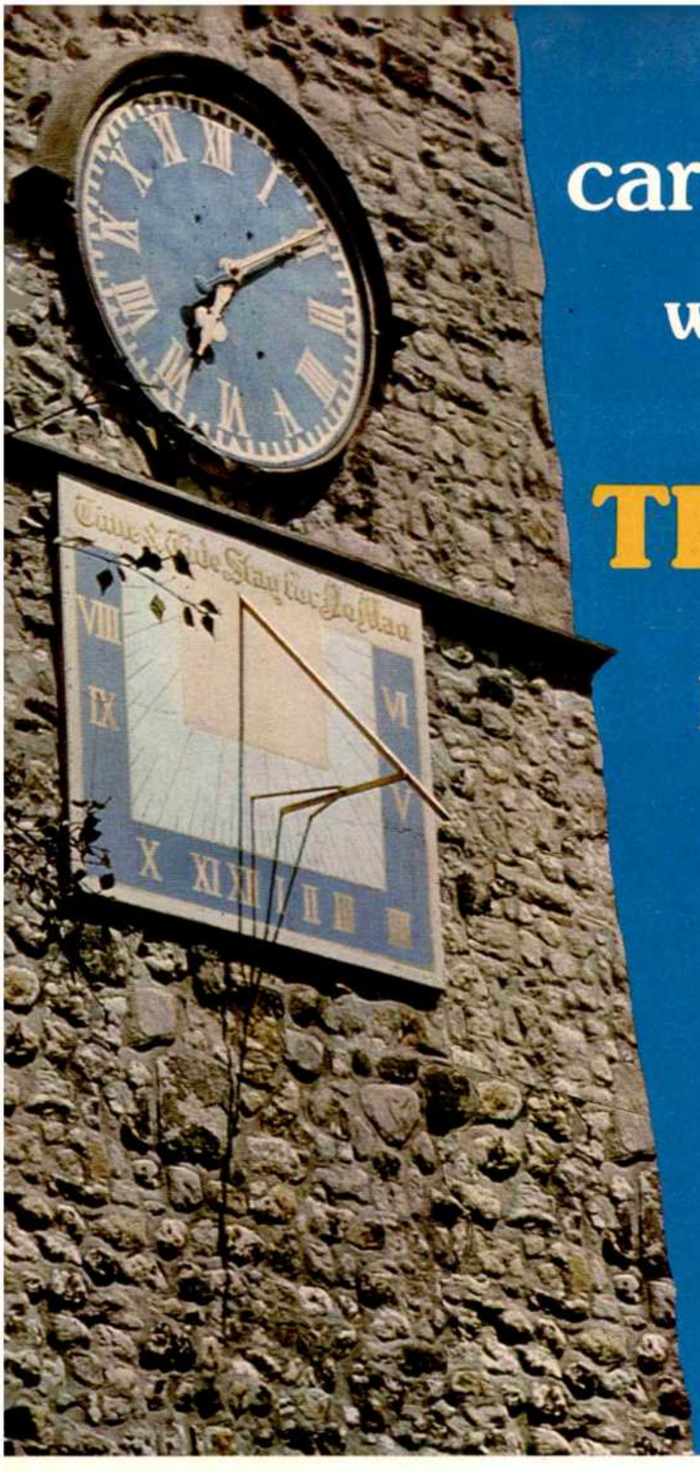

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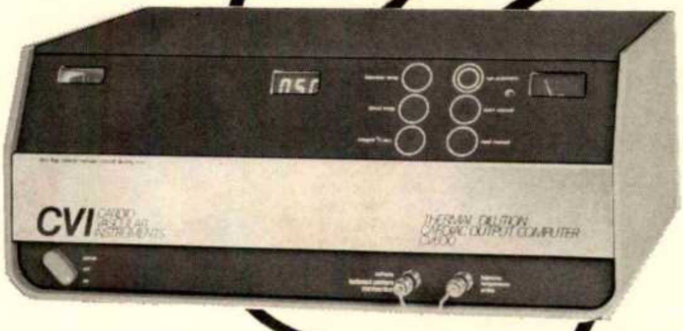
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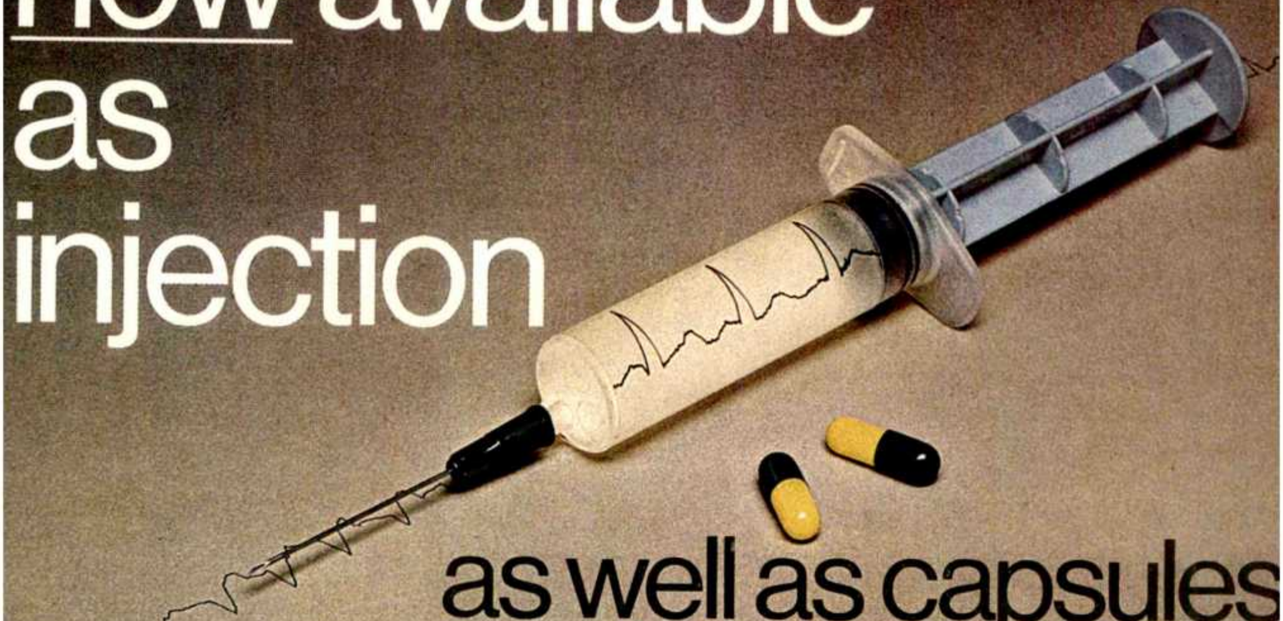

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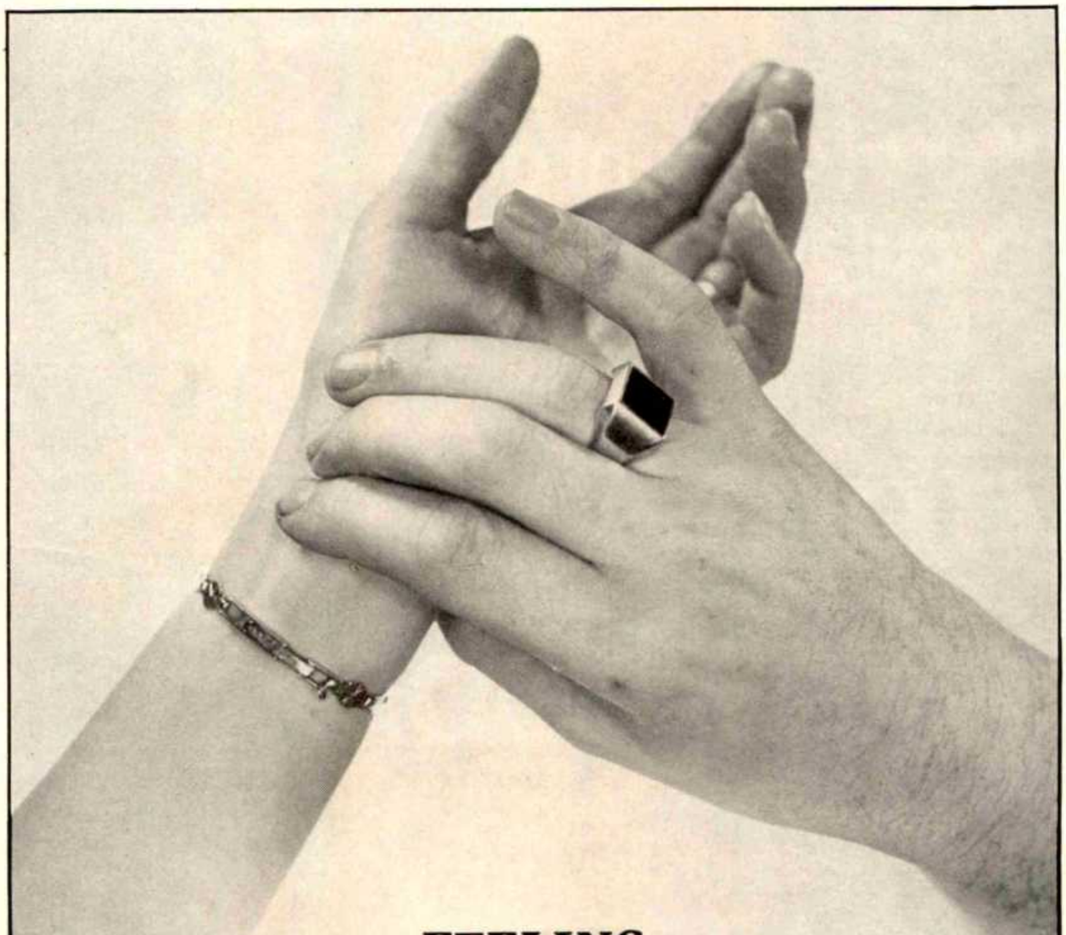

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THE ADULT POSTOPERATIVE CHEST *by* **Myron Melamed; Florencio A. Hipona,** *Harvard Medical School, Boston, Massachusetts;* **Carlos J. Reynes,** *Loyola Univ. Medical School, Maywood, Illinois;* **Walter L. Barker,** *Univ. of Illinois, Chicago, Illinois: and* **Santiago Paredes,** *Boston Univ. School of Medicine, Boston, Massachusetts. Foreword by* **Hiram T. Langston.** This study of adult pulmonary and cardiovascular radiography after surgery systematically assesses the extraneous factors imposed upon x-ray film by the surgical act. Brief comments about behavior of the pleura, lung redistribution and postoperative function are also included. *'77, 396 pp., 578 il., 1 table, $31.50*

SYNTHETIC FIBRINOLYTIC THROMBOLYTIC AGENTS: Chemical, Biochemical, Pharmacological and Clinical Aspects *edited by* **K. N. von Kaulla,** *Univ. of Colorado Medical Center, Denver, Colorado, and* **J. F. Davidson,** *Royal Infirmary, Glasgow, Scotland.* The present knowledge of the physiology of the human fibrinolytic system and its function or malfunction in relation to thrombosis is reviewed in this text along with synthetic compounds capable of activating the fibrinolytic system. Desirable properties of an optimal antithrombotic agent are defined and methods used for assessing the fibrinolytic activity of such an agent *in vitro* and *in vivo* are discussed. *'75, 528 pp. (6 3/4 x 9 3/4), 253 il., 86 tables, $34.50*

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NEWBORN INTENSIVE CARE: Chemical Aspects *by* **Toshiko Hirata** *and* **June P. Brady,** *both of Univ. of California, San Francisco, California. Forewords by* **Moses Grossman** *and* **I. Newton Kugelmass.** Basic physiologic and chemical processes occurring in the fetus and newborn infant are explored and analyzed. Topics emphasized include the treatment of those problems most common in newborn infants, the effects of drugs on the fetus and neonate, and the unique physiology of the preterm infant. Basic information on cardiopulmonary adaptation and dysadaptation, and on the control of respiration, body fluids, electrolyte balance, temperature regulation and renal function is also presented. *'77, 196 pp., 25 il., 14 tables, $16.75*

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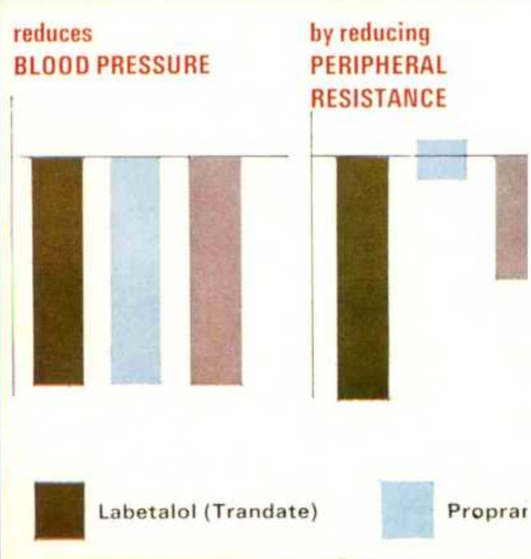

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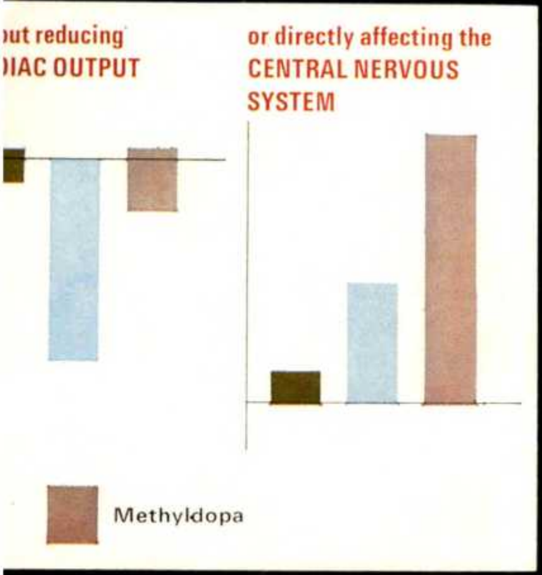

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Brit. J. clin. Pharmacol., 1976, 3 (Suppl.3), 757

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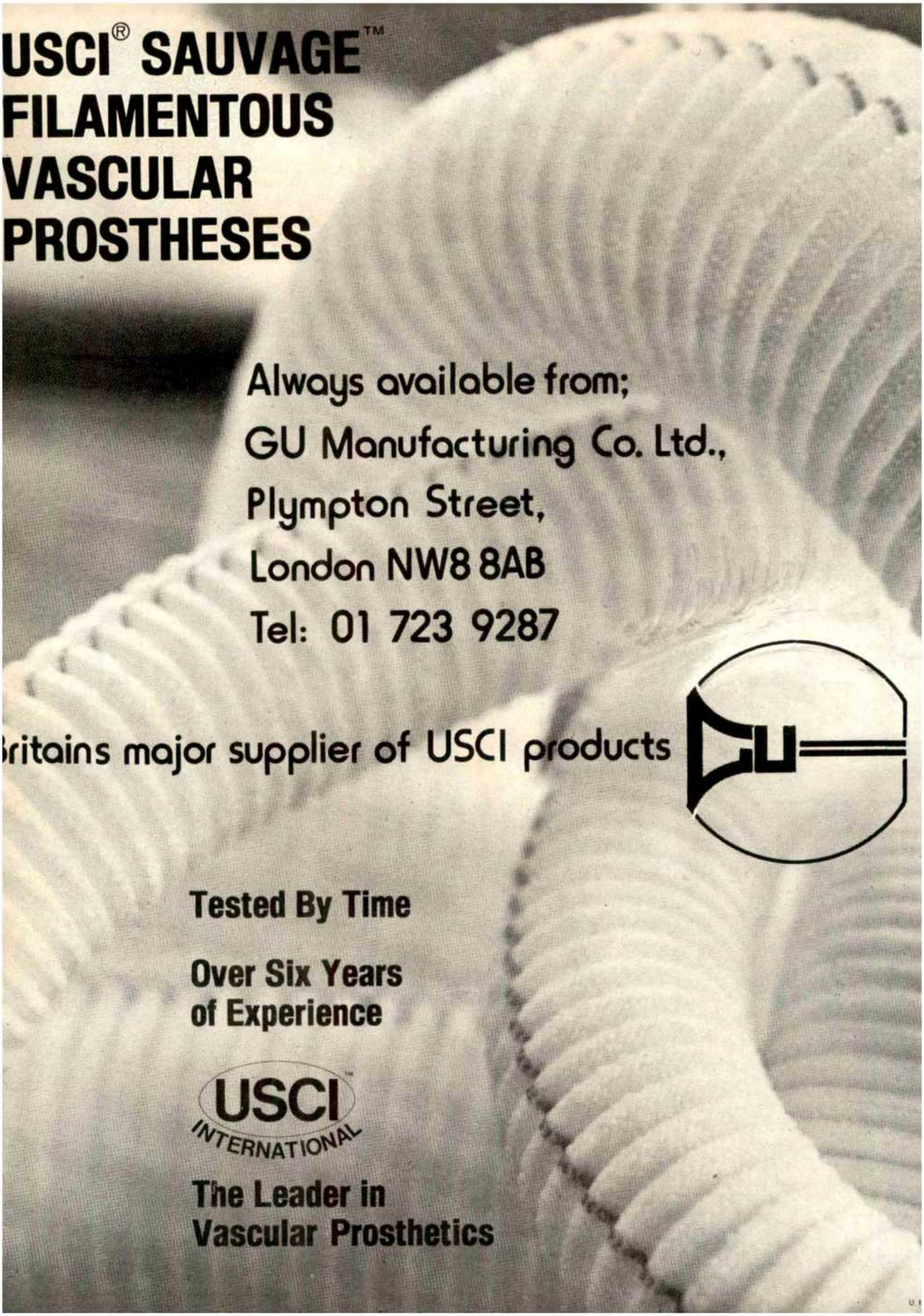

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1. Lancet, 1973, ii, 399 2. Lancet, 1973, ii, 404 3. Amer. Heart J., 1976, *91*, 58
4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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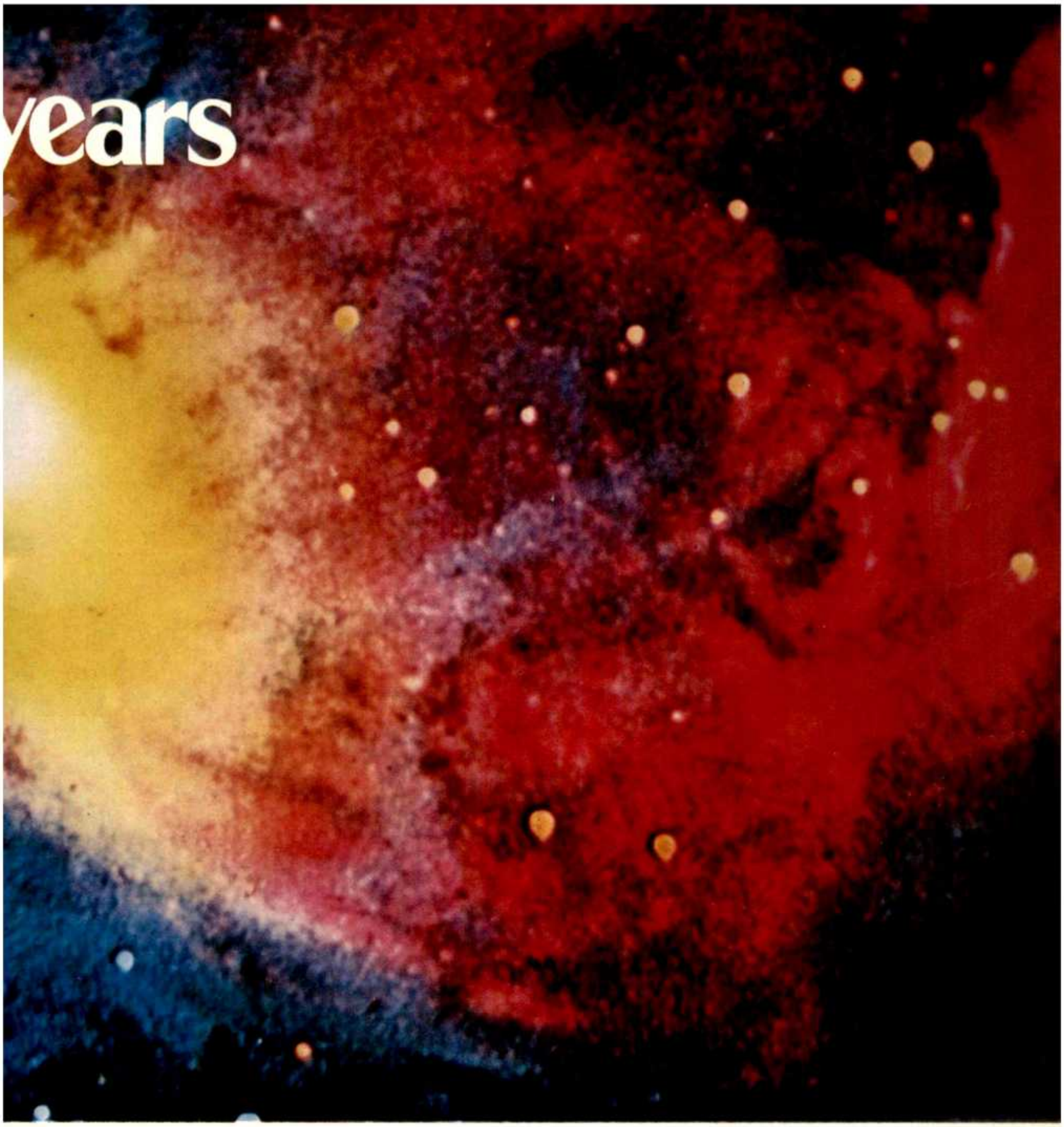

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References 1. *Concepts in the treatment of hypertension*, *Excerpta Medica*, Amsterdam, 1977, p.66.
2. *Europ. J. Clin. Pharmacol.*, 1976, **10**, 375

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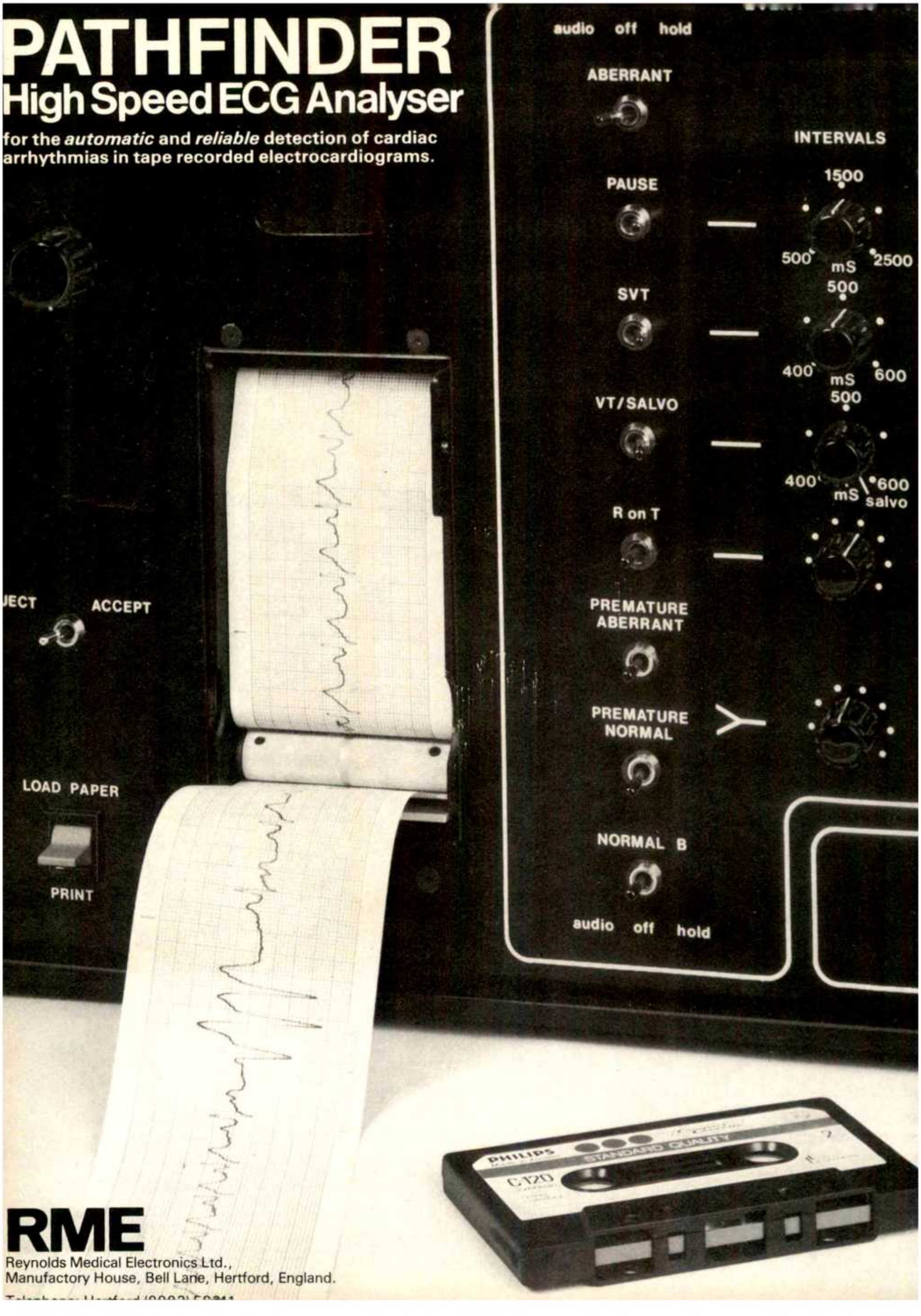

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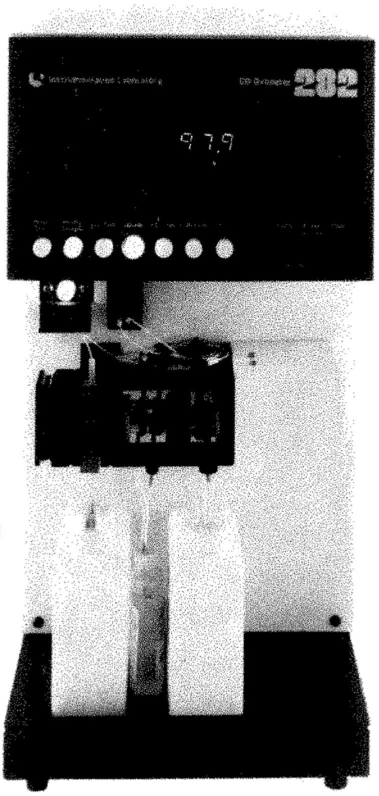

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British Heart Journal, 1977, **39**, 1163–1166

Prognosis of patients with acute myocardial infarction admitted to a coronary care unit
I: Survival in hospital

A. H. KITCHIN AND S. J. POCOCK

From the Department of Medicine, University of Edinburgh, Western General Hospital; and Medical Computing and Statistics Group, Edinburgh University Medical School

On a basis of history, clinical examination, and the electrocardiogram it was possible to identify groups of patients with acute myocardial infarction with good and bad prognoses as regards hospital survival. Individual adverse factors were age, previous history of ischaemic heart disease, anterior infarction, persistent sinus tachycardia, pulmonary crepitations, hypotension, and raised venous pressure. Multivariate analysis showed four factors remaining significant—age, tachycardia, hypotension, and pulmonary crepitations. As a result of treatment of cardiac arrest, hospital mortality, which would otherwise have been 20 per cent, was 17 per cent. Preceding unstable angina did not worsen the immediate prognosis.

With the opening of a coronary care unit in this district general hospital in 1966, a prospective study was planned of factors affecting survival of male patients with acute myocardial infarction. Patients were admitted to the study during the 3 years 1966 to 1969 and followed up subsequently for periods of up to 7½ years.

Patients and methods

Of 872 male patients under 70 years admitted to the unit, 508 had acute myocardial infarction confirmed on a basis of two or more of the following criteria:— (1) History of severe central chest pain lasting for more than 2 hours; (2) classical electrocardiographic abnormalities of recent infarction, or ST-T changes and increase in blood AST level; (3) left bundle-branch block and rise in blood AST level. Some patients who died early after admission were included on necropsy evidence only. The remainder had angina (143), other cardiovascular conditions (104), and miscellaneous respiratory, gastro-intestinal, or musculoskeletal pains. The clinical features of patients included in the study are shown in Table 1.

Local general practitioners were approached and invited to seek admission directly to the unit of all patients suspected of having sustained a recent infarct. Doctors and nurses working in the unit used an agreed therapeutic schedule. Patient data were recorded on specially designed proformata. Patients were treated in the unit for periods of 2 to 10 days (average 4). The estimated interval between the onset of infarction and admission to the unit was under 6 hours in 56 per cent, 6 to 24 hours in 28 per cent, and over 24 hours in 16 per cent. The mean time was 4 hours. Serial data recorded included heart rate, blood pressure, fluid balance, occurrence of arrhythmias, clinical observations of venous pressure, pulmonary crepitations, ausculatory findings in the heart, and complications.

Received for publication 13 April 1977

Results

(1) DEATHS IN HOSPITAL

Sixty-four patients (12·6%) died in the coronary care unit and a further 24 (4·7%) during the remainder of their hospital stay. Total hospital deaths were therefore 88 or 17 per cent of patients admitted. Mortality was significantly related to several factors determined at the time of admission (Table 1). Age 60 or over, a low systolic blood pressure or sinus tachycardia maintained over 4 hours, increased venous pressure, and pulmonary crepitations were all associated with a higher mortality rate. A previous history of ischaemic heart disease also indicated a poorer hospital prognosis especially if the patient had had a previous infarct but gave no history of angina. The fact that heavy smokers had a significantly lower hospital mortality may be partly explained by the tendency for heavy smokers to be younger (69% aged under 60, versus 52% of the other patients).

A multivariate analysis, using linear logistic regression (Cox, 1970), was carried out in order to assess simultaneously the prognostic value of all these factors. This analysis shows that only 4 factors then have statistically significant regression coefficients; these are high pulse rate ($P < 0{\cdot}001$), low blood pressure ($P < 0{\cdot}01$), pulmonary crepitations ($P < 0{\cdot}02$), and age over 60 ($P < 0{\cdot}01$). It is of interest to note that the initial clinical assessment by the attending physician at the time of admission was a very reliable prognostic indicator with only 4 per cent of patients with 'good prognosis' dying in hospital compared with 67 per cent of those with 'poor prognosis'.

Premonitory symptoms

Unstable angina in the period 2 months to 1 day preceding infarction was reported by 37 per cent. This group of patients had hypotension significantly less commonly after infarction (46% versus 57%; $P < 0{\cdot}05$) and more often gave a family history of ischaemic heart disease (37% versus 26%; $P < 0{\cdot}05$). They did not have a significantly higher mortality (Table 1; Fulton *et al.*, 1972).

Anterior myocardial infarction

Patients with anterior infarction had a higher mortality than those with inferior infarction (Table 2). Anterior infarction was significantly associated with sinus tachycardia (46% versus 33%; $P < 0{\cdot}005$) and presence of a third or fourth

Table 1 *Hospital mortality and patient characteristics on admission*

Characteristic	*Level*	*No. of patients*	*No. (and %) dying in hospital*	*P value**
All patients		508	88 (17%)	
Age (y)	< 40	20	0 (0%)	< 0·001
	40–49	87	11 (13%)	
	50–59	188	23 (12%)	
	60–69	193	48 (25%)	
	70 +	20	6 (30%)	
Previous history of ischaemic heart disease	None	231	27 (12%)	< 0·001
	Angina only	139	27 (19%)	
	Infarct only	46	15 (33%)	
	Both infarct and angina	92	19 (21%)	
Preinfarction crescendo angina	No	320	57 (18%)	NS
	Yes	188	31 (16%)	
Previous history of hypertension	No	442	71 (16%)	NS
	Yes	61	14 (23%)	
		5	3	
Family history of ischaemic heart disease	No	322	51 (16%)	NS
	Yes	140	16 (11%)	
	Unknown	46	21	
Smoking history	Non-smoker	113	21 (16%)	= 0·05
	Moderate	164	27 (16%)	
	Heavy	202	22 (11%)	
	Unknown	29	18 —	
Delay in admission	< 6 hours	286	50 (17%)	NS
	6–24 hours	141	26 (18%)	
	24 + hours	81	12 (15%)	
Lowest systolic BP (mmHg) > 4h	⩾ 100	237	25 (11%)	< 0·001
	< 100	271	63 (23%)	
Highest pulse rate > 4h	⩽ 100	306	37 (12%)	< 0·001
	> 100	202	51 (25%)	
Third or fourth heart sound	No	330	50 (15%)	NS
	Yes	163	27 (17%)	
	Unknown	15	11	
Mitral systolic murmur	No	440	65 (15%)	< 0·1
	Yes	53	12 (23%)	
	Unknown	15	11	
Raised venous pressure	No	308	41 (13%)	< 0·01
	Yes	190	40 (22%)	
	Unknown	10	7	
Pulmonary crepitations	No	247	23 (9%)	< 0·001
	Yes	250	58 (23%)	
	Unknown	11	7	
Obesity	No	291	55 (22%)	NS
	Yes	199	29 (19%)	
	Unknown	18	4	
Initial clinical assessment	Good	260	11 (4%)	< 0·001
	Fair	164	21 (13%)	
	Poor	84	56 (67%)	

*Significance levels based on standard χ^2 tests for comparison of percentages except for age when a test for trend in percentage was used.

Table 2 *Electrocardiographic abnormalities and hospital mortality*

		No. of patients	*No. (and %) dying in hospital*	*P value*
Position	Anterior	258	45 (17%)	0·02
	Inferior	220	23 (10%)	
	None/unknown	30	20	
Q wave	Yes	347	55 (16%)	0·08
	No	135	14 (10%)	
	Unknown	26	19	

heart sound (38% versus 25%; $P<0{\cdot}05$) while inferior infarcts were associated with venous pressure increase (45% versus 34%; $P<0{\cdot}05$).

Transmural infarction
Presence of pathological Q waves was associated with sinus tachycardia (46% versus 30%; $P<0{\cdot}005$) and arrhythmias (42% versus 28%; $P<0{\cdot}005$). It was commoner in inferior than in anterior infarcts (50% versus 39%; $P<0{\cdot}1$). There was a marginally significant difference, however, as regards survival in hospital, compared with patients with intramural infarction (Table 2).

(2) COURSE IN HOSPITAL
The frequency of various clinical observations in patients in the coronary care unit is shown in Table 3.

Arrhythmias
Arrhythmias (excluding asystole) requiring treatment according to defined criteria occurred in 39 per cent of cases. The order of frequency was persistent ventricular extrasystoles, ventricular fibrillation, atrial fibrillation or flutter, atrioventricular block, sinus bradycardia, atrial tachycardia, and ventricular tachycardia. Arrhythmias were significantly commoner in patients with a previous infarct (50% versus 36%; $P<0{\cdot}005$) and in patients with pulmonary crepitations and hypotension (49% versus 28%; $P<0{\cdot}001$). Atrioventricular block was commoner in inferior than in anterior infarcts (8% versus 1%; $P<0{\cdot}001$). Sinus bradycardia did not predispose to ventricular arrhythmias or worsen prognosis (Table 1; Epstein *et al.*, 1973).

Table 3 *Frequency of complications*

Frequency of complications	
Persistent sinus tachycardia	47%
Hypotension (< 100 mmHg)	47%
Cardiac failure—triple rhythm	32%
venous presssure +	37%
pulmonary oedema	30%
Mitral systolic murmur	10%
Arrhythmia requiring treatment	39%
supraventricular	16%
ventricular (not VF)	15%
bradyarrhythmia	7%
Cardiac arrest—85 cases of whom 25 survived	17%

Cardiac arrest
Cardiac arrest occurred in 85 (17%) of cases, 38 from ventricular fibrillation and 47 from asystole. Only 2 patients with asystole were successfully resuscitated. Twenty-three patients with ventricular fibrillation were resuscitated, but of these only 12 survived to leave hospital. The majority of arrests occurred in patients with a combination of pulmonary crepitations and hypotension, and this group (145 in number) had a high hospital mortality of 30 per cent. Only 14 out of the 44 patients in this group who arrested were resuscitated, and none survived to leave hospital.

Time of onset of symptoms
Where admission to the coronary care unit was delayed beyond 6 hours after the onset of symptoms the frequency of cardiac arrest fell from 19 per cent to 4 per cent and of death in the coronary care unit from 14 per cent to 11 per cent. This presumably reflects the high early mortality from arrhythmia. In the few cases where admission was delayed beyond 24 hours the figures were 10 per cent and 7 per cent, respectively. However, there was no significant effect of delayed admission on overall hospital mortality (Table 1).

AST levels
These appeared to relate well to other measures of severity. Of 144 patients with AST greater than 100, 48 per cent had persisting sinus tachycardia, 62 per cent had hypotension, and 46 per cent had raised venous pressure compared with 36 per cent, 45 per cent, and 35 per cent, respectively, of 302 patients with lesser levels of AST ($P<0{\cdot}1$, $0{\cdot}001$, $0{\cdot}05$). Higher levels were commoner in transmural than in intramural infarcts (36% versus 19%; $P<0{\cdot}005$).

Discussion

The present survey confirms the findings of others as regards the unfavourable effects on immediate mortality in the coronary care unit of increasing age and signs of heart failure or hypotension, and the neutral effects of previous high blood pressure, pre-infarction crescendo angina, and obesity.

In some respects differences were found. Anterior infarcts were related to a higher mortality than inferior, confirming the finding of Norris *et al.* (1973) and at variance with those of Doscher and Poindexter (1950) and Beard *et al.* (1960). Norris *et al.* found a difference between transmural and intramural infarction, whereas Scheinman and Abbott (1973) did not; the present study gave only marginal support to the former. A past history of angina had an unfavourable effect in this study as in the series of Doscher and Poindexter (1950), Frank *et al.* (1973), and Norris *et al.* (1973), while Kannel and Feinleib (1972) and Chapman (1972) have found no such adverse effect. However, the present study showed that a previous infarct without angina led to an even worse prognosis.

It has to be said that the number of lives saved by electrical treatment of cardiac arrest was small (3%) in relation to the total number of patients. Clearly, however, an additional unknown number of patients may have been saved in the coronary care unit by prophylactic treatment of arrhythmia and early treatment of cardiac failure.

It would be useful to identify categories of patients with myocardial infarction who have a good prognosis and who would not benefit significantly from treatment in a coronary care unit. In this series the number of hospital deaths together with successfully treated cardiac arrests which would have been fatal outside hospital represented 20 per cent of all cases. Review of the data shows that subgroups might have been identified on a basis of data available at the time of admission who proved to have a lower risk of cardiac arrest and death, the main factors being a younger age, absence of past history of angina or infarction, absence of pulmonary crepitations or hypotension, and a heart rate below 100 per minute. For example, of the 101 patients aged under 60 with no hypotension and no previous infarct only 7 per cent died or had a cardiac arrest in hospital.

The design of this study included an estimate of prognosis by the admitting registrar on the basis of history and examination. This proved a surprisingly accurate indication of the risk of dying from acute infarction.

References

Beard, O. W., Hipp, H. R., Robins, M., Taylor, J. S., Ebert, R. V., and Beran, L. G. (1960). Initial myocardial infarction among 503 veterans. *American Journal of Medicine*, **28**, 871–883.

Chapman, B. L. (1972). Relation of cardiac complications to SGOT level in acute myocardial infarction. *British Heart Journal*, **34**, 890–896.

Cox, D. R. (1970). *The Analysis of Binary Data*, pp. 87–91. Methuen, London.

Doscher, N., and Poindexter, C. A. (1950). Myocardial infarction without anticoagulent therapy. *American Journal of Medicine*, **8**, 623–633.

Epstein, S. E., Goldstein, R. E., Redwood, D. R., Kent, K. M., and Smith, E. R. (1973). The early phase of acute myocardial infarction. *Annals of Internal Medicine*, **78**, 918–936.

Frank, C. W., Weinblatt, E., and Shapiro, S. (1973). Angina pectoris in men; prognostic significance of selected medical factors. *Circulation*, **47**, 509–517.

Fulton, M., Duncan, B., Lutz, W., Morrison, S. L., Donald, K. W., Kerr, F., Kirby, B. J., Julian, D. G., and Oliver, M. F. (1972). Natural history of unstable angina. *Lancet*, **1**, 860–865.

Kannel, W. B., and Feinleib (1972). Natural history of angina pectoris in the Framingham study. *American Journal of Cardiology*, **29**, 154–163.

Norris, R. M., Caughey, D. E., Deeming, L. W., Mercer, C. J., and Scott, P. J. (1973). Prognosis following acute myocardial infarction. *New Zealand Medical Journal*, **77**, 12–18.

Scheinman, M. M., and Abbott, J. A. (1973). Clinical significance of transmural versus non-transmural electrocardiographic changes in patients with acute myocardial infarction. *American Journal of Medicine*, **55**, 602–607.

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Prognosis of patients with acute myocardial infarction admitted to a coronary care unit

II: Survival after hospital discharge

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The factors adversely affecting long-term prognosis differed from those affecting outcome of acute infarction. Individual factors were previous history of infarction or of hypertension, tachycardia, cardiac arrest, ventricular arrhythmia, atrial fibrillation, 3rd heart sound, raised venous pressure, and pulmonary crepitations. Multivariate analysis reduced these to 6—previous infarct or hypertension, sinus tachycardia, cardiac arrest, ventricular arrhythmia, and atrial fibrillation. Of those who survived 5 years, approximately half had angina. Two-thirds of the under 60 survivors were at their normal work.

The patient population under observation in this study has been described in the previous paper by Kitchin and Pocock. In brief, 872 patients were admitted directly to the coronary care unit at the Western General Hospital, Edinburgh, during the period April 1966 to April 1969, and of these 508 (58%) were judged to have sustained an infarct. This paper is concerned with the prognosis of patients on leaving hospital, so that the 63 deaths in the coronary care unit and the 25 deaths of patients still in hospital after leaving the coronary care unit are excluded. There remains a total of 420 patients with myocardial infarction who left hospital and were followed for periods of 5 to 7 years. This is the population to be examined for long-term prognosis.

Methods

Ancillary information regarding previous history of disease, signs and symptoms upon admission to the coronary care unit, and other background information (e.g. age, smoking history) were collected on a standard proforma.

Survival follow-up was achieved through either the hospital outpatient clinic or the patient's general practitioner, except for 20 patients who had left the district whose survival was established by the Registrar General's department. A total of 151 deaths was reported. For the patients who survived 5 years, a standard proforma on the patient's state of health at that time was completed by the general practitioner. The questions asked concerned the recurrence of myocardial infarction, the presence and severity of angina and breathlessness, diuretic therapy, and occupational status. Since these proformas were collected at fixed 2-yearly dates the exact follow-up time of this information varied from 4 to 6 years. Seventy-eight per cent of proformas were completed satisfactorily by the general practitioner and for the remainder a simplified proforma was sent directly to the patient's home. There remained 23 who survived for 5 years (8%) for whom this information was unobtainable, and a small number of others with only partial information.

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Results

OVERALL SURVIVAL

Fig. 1 shows the survival curve for all 420 patients who left hospital. Since patients were followed for varying periods (5 to 7 years) the life-table method (Cutler and Ederer, 1958) has been applied in all the survival plots presented in this paper. Fig. 1 also shows the survival experience of myocardial infarcts described in 4 previous studies, and it can be seen that the experience in this study is broadly similar. One hundred and twenty-five patients (30%) died within 5 years and an estimated 40 per cent died within 7 years.

The death rate was fairly constant during the first 2½ years at an average of 8·6 per cent per annum which is significantly higher than the average 5·5 per cent per annum during the next 2½ years ($P < 0{\cdot}05$). This suggests that prognosis improves somewhat once the patient has survived the first 2½ years after an infarct.

For those dying within 5 years the primary causes of death were: myocardial infarct (78), other cardiovascular diseases (11), cancer (3), other causes (4), and not known (29).

Table 1 *Long-term survival and patient characteristics*

Characteristic	*Level*	*No. of patients*	*No. (%) dead within 5 years*
Age (y)	< 40	20	4 (20%)
	40–49	76	18 (24%)
	50–59	165	52 (32%)
	60–69	145	43 (30%)
	70 +	14	8 (57%)
Previous history Angina	Yes	185	64 (35%)
	No	235	61 (26%)
Preinfarction crescendo angina	Yes	157	42 (27%)
	No	263	83 (32%)
Myocardial infarction	Yes	104	46 (44%)***
	No	316	79 (25%)
Hypertension	Yes	47	23 (49%)**
	No	371	101 (27%)
	Unknown	2	
Family history of myocardial infarction	Yes	124	43 (35%)
	No	271	72 (27%)
	Unknown	25	
Electrocardiographic abnormality			
Position	Anterior	213	66 (31%)
	Inferior	197	54 (27%)
	None/ Unknown	10	
Q wave	Yes	292	92 (32%)
	No	121	31 (26%)
	Unknown	7	
AST enzyme rise	< 40	115	30 (26%)
	40–100	156	48 (31%)
	> 100	125	39 (31%)
	Unknown	24	
Lowest systolic blood pressure	≥100	212	66 (31%)
	< 100	208	59 (28%)
Highest pulse rate	< 100	269	55 (20%)***
	≥100	151	70 (46%)
Cardiac arrest	Yes	16	10 (63%)**
	No	404	115 (28%)
Arrhythmias			
Bradyarrhythmias	Yes	30	8 (27%)
	No	390	117 (30%)
Ventricular arrhythmias	Yes	68	32 (47%)**
	No	352	93 (26%)
Atrial fibrillation	Yes	21	14 (67%)***
	No	399	111 (28%)
Supraventricular arrhythmias (including atrial fibrillation)	Yes	31	14 (45%)
	No	389	111 (29%)
Third or fourth heart sound	Yes	136	49 (36%)*
	No	280	73 (26%)
	Unknown	4	
Mitral systolic murmur	Yes	41	17 (41%)
	No	375	105 (28%)
	Unknown	4	
Raised jugular venous pressure	Yes	149	55 (37%)*
	No	268	67 (25%)
	Unknown	3	
Pulmonary crepitations	Yes	192	68 (35%)**
	No	224	53 (24%)
	Unknown	4	
All patients		420	125 (30%)

*$P < 0{\cdot}05$
**$P < 0{\cdot}01$
***$P < 0{\cdot}001$
Indicates a significant difference in the percentages surviving 5 years, based on standard χ^2 tests.

LONG-TERM SURVIVAL AND PATIENT CHARACTERISTICS

There were several characteristics recorded about each patient after admission to the coronary care unit. In order to examine which characteristics are associated with long-term survival, Table 1 shows the percentage dead within 5 years for patients classified by each characteristic.

The following characteristics were associated with a significantly poorer survival record after 5 years: previous history of myocardial infarction or hypertension, highest pulse rate ≥100 (2 or more consecutive 4-hourly recordings), cardiac arrest, ventricular arrhythmia, atrial fibrillation, third or fourth heart sound, raised jugular venous pressure, and pulmonary crepitations. In addition 4 other characteristics (namely age, previous angina, family history, and mitral systolic murmur) may possibly have some impact on long-term survival, though their associations were not quite formally significant.

A PROGNOSTIC INDICATOR FOR SURVIVAL

The results presented in Table 1 give some idea as to the many factors which influence the patient's survival after leaving hospital. However, the scope of this information is limited by the fact that each factor was considered separately so that the overall *combined* impact of these factors could not be properly assessed. Therefore, in order to obtain a more accurate prognosis for any individual patient, with his multitude of potentially relevant characteristics, one must consider a multivariate statistical analysis of survival.

Thus, when all the characteristics listed in Table 1 are considered collectively, it turns out that only 6 of them significantly influence a patient's chances of surviving 5 years. These 6 prognostic factors are previous myocardial infarct, previous hypertension, pulse rate ≥100, cardiac arrest, ventricular arrhythmia, and atrial fibrillation. This result has been obtained using the maximum likelihood solution of a linear-logistic model for the probability of surviving 5 years (see Cox, 1970) and leads to the following prognostic indicator.

Let P be the probability of a patient surviving 5 years. Then

$$
\begin{array}{rl}
\ln \dfrac{P}{(1-P)} = +1{\cdot}842 & \\
-0{\cdot}846 & \text{If previous myocardial infarct} \\
-0{\cdot}998 & \text{If previous hypertension} \\
-0{\cdot}903 & \text{If highest pulse rate} \geqslant 100 \\
-1{\cdot}215 & \text{If cardiac arrest} \\
-0{\cdot}630 & \text{If ventricular arrhythmia} \\
-1{\cdot}353 & \text{If atrial fibrillation}
\end{array}
$$

where $\ln \dfrac{P}{(1-P)}$ is the natural logarithm of the odds of surviving 5 years. For example, if a patient has none of these 6 characteristics then $\ln \dfrac{P}{(1-P)} = 1{\cdot}842$ and P, the probability of surviving 5 years $= 0{\cdot}86$. If a patient has a previous infarct and highest pulse rate $\geqslant 100$ but none of the other characteristics then

$$\ln \frac{P}{(1-P)} = +1{\cdot}842 - 0{\cdot}846 - 0{\cdot}903 = +0{\cdot}093 \text{ and}$$

$P = 0{\cdot}52$. Similarly, provided one knows which of these 6 characteristics are present for a patient, one can then predict his chances of surviving 5 years.

The accuracy of this prognostic indicator has been thoroughly tested using a variety of statistical procedures and the authors have concluded that it is the best predictor that could be derived from the experience of the 420 patients analysed. Of course, it is based on a particular coronary care unit and, therefore, some degree of caution would be advisable in applying the predictor to any other population except as a general guideline.

It is evident that cardiac arrest and atrial fibrillation make the greatest contribution to the prognostic indicator whereas ventricular arrhythmia, with the smallest coefficient in the formula above, makes the least contribution out of the 6 patient characteristics. However, all the 6 coefficients are of a similar order of magnitude so that without any great loss of information one could express the survival prognosis of a patient simply by the number of these characteristics he has experienced. For instance, Fig. 2 shows the survival curves for patients categorised according to this number of unfavourable characteristics. Evidently, there is considerable discrimination between the 4 groups of patients throughout the 7-year period of follow-up. In particular, the 5-year percentages surviving are 86, 72, 52, and 27, for those with none, 1, 2, and 3 or more characteristics, respectively.

HEALTH AND EMPLOYMENT STATUS AFTER 5 YEARS

The results now described were collected on a standard proforma mostly from the patient's general practitioner at some time between 4 and 6 years after leaving hospital (see methods above for further details). Table 2 shows the replies obtained for the 295 5-year survivors. These results from a survivor population have the obvious limitation that most of the more severely affected will have already died, but there are one or two interesting features worthy of comment.

At 5 years 7 per cent of survivors reported probable and another 9 per cent possible recurrences of infarction. Of 57 patients who had given a past history of infarction, 30 per cent had probable or possible recurrence.

Angina was reported after 5 years in 121 (45%) of survivors. Of the 115 with angina before the infarct 5 years before, 73 (63%) still had angina, whereas of the 156 without previous angina only 48 (31%) were now affected ($P < 0{\cdot}001$).

Shortness of breath was reported by 47 per cent of the 5-year survivors. This increased to 62 per cent if they had had heart failure in the form of pulmonary crepitations at the time of infarction as

Table 2 *Health and employment status for 5-year survivors (295 patients)*

		No. of patients (% ignoring unknowns)
Recurrence of myocardial infarct within the 5-year period	No	224 (84%)
	Possible	24 (9%)
	Probable	20 (7%)
	Unknown	27
Angina now present	None	150 (53%)
	Mild	70 (25%)
	Moderate	36 (13%)
	Severe	15 (5%)
	Unknown	24
Breathlessness now present	None	141 (53%)
	Mild	68 (26%)
	Moderate	42 (16%)
	Severe	14 (5%)
	Unknown	30
Currently receiving diuretic therapy	No	232 (86%)
	Yes	38 (14%)
	Unknown	25
Current employment status	Returned to normal work	102 (65%)
	Lighter job	31 (20%)
	Can't find job	11 (7%)
	Unable to work	14 (9%)
	Unknown or inapplicable	137

compared with 39 per cent of those who did not ($P < 0.001$).

The question about employment status was considered applicable only to men under age 60. Those under age 50 had fared somewhat better than those in their 50's with 75 per cent at their normal work compared with 57 per cent ($P < 0.05$). There was also a strong relation between employment status and presence of angina since 72 per cent of those without angina were at their normal work compared with only 45 per cent of those with moderate or severe angina ($P < 0.01$).

Discussion

The 5-year survival rate in the present series for male patients who survived to leave hospital after acute myocardial infarction was 70 per cent and for patients with first infarcts it was 75 per cent. Fig. 1 shows a comparison of these results with the results of 4 other studies, the Health Insurance Plan of New York (Frank *et al.*, 1973) who found a survival rate of 81 per cent at 4½ years for patients with first infarcts, the Oslo Diet Study of Leren (1970), the series of Zukel *et al.* (1969) relating to army personnel in the war, and the Mayo Clinic series of Juergens *et al.* (1960). The study of Honey and Truelove (1957) in Oxford patients showed a 61 per cent survival rate at 5 years and Pell and D'Alonzo (1964) reported a 74 per cent survival rate at 5 years in male employees surviving a first infarct. The findings of the present study are, therefore, intermediate in position. The Health Insurance Programme Study was a prospective one and therefore likely to include milder cases. The same applies to Zukel's study of army personnel who were younger and, in some cases, asymptomatic. Here, however, a high mortality was reported during the first year.

Several of these studies have identified factors associated with a poor long-term prognosis. The Health Insurance Programme Study identified a previous history of hypertension and of angina pectoris as unfavourable factors. Pell and D'Alonzo found that increasing age and a previous history of hypertension were unfavourable. Leren found that a previous history of myocardial infarction or of hypertension worsened the long-term prognosis. The Veterans' Administration Study of Beard *et al.* (1960) who found a 69 per cent survival at 5 years after first infarction, identified the factors of age, previous hypertension or angina, cardiac failure at the time of infarction, serious arrhythmia at the time of infarction, and high fever after myocardial

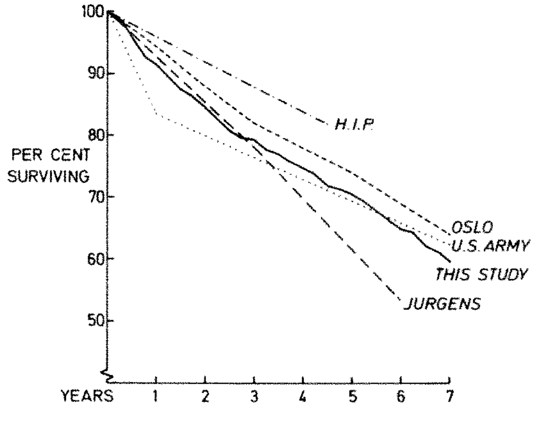

Fig. 1 *Long-term survival after leaving hospital for 420 patients, compared with 4 previous studies. Health Insurance Programme (H.I.P.) (Frank* et al., *1973); Oslo Diet-Heart Study (Leren, 1970); Zukel* et al. *(1969); Juergens* et al. *(1960).*

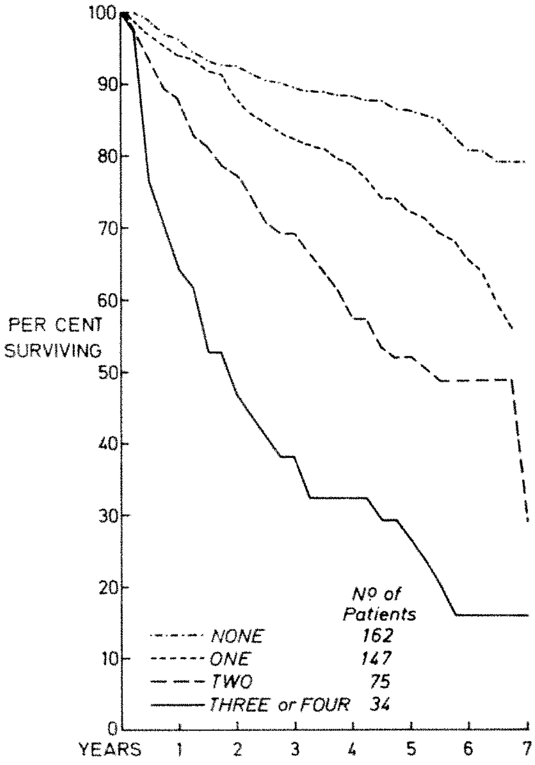

Fig. 2 *Long-term survival related to presence or absence of 6 unfavourable characteristics.*

infarction as unfavourable prognostic factors. Norris and his co-workers (1974) have studied survival over a 3-to-6-year period after myocardial infarction. They found hypertension to be adverse, and confirmed the adverse effect of increasing age and previous history of infarction and of the occurrence of signs of cardiac failure at the time of infarction. Anterior transmural infarcts carried a slightly worse prognosis than inferior (Norris and Mercer, 1973) and the occurrence of ventricular arrhythmias during the acute infarct also carried a bad prognosis though the authors argued that this factor did not stand on its own but merely reflected the presence of other adverse features.

In the present data a previous history of myocardial infarction or hypertension, sinus tachycardia, atrial fibrillation, third heart sound, raised venous pressure, pulmonary crepitations, ventricular arrhythmia, and occurrence of cardiac arrest were all found to be individual factors associated with poorer prognosis. It is clear that many of these factors, which have been individually identified, are associated with one another, as for example various manifestations of left ventricular failure, previous myocardial damage or deranged myocardial metabolism or electrophysiology. An attempt has, therefore, been made by multifactorial analysis to pick out factors which exert an independent adverse effect on long-term prognosis. Of the 6 factors identified in the present data, i.e. previous myocardial infarction or hypertension, sinus tachycardia or atrial fibrillation, ventricular arrhythmia or cardiac arrest occurring during the course of the acute infarction, only atrial fibrillation has not been mentioned in other series. Though it occurred in a relatively small number of cases it was associated with a very poor 5-year survival. Persistent sinus tachycardia after infarction was found by Norris and Mercer (1973) to be an unfavourable prognostic sign while previous myocardial infarction and hypertension are recognised in nearly all series as being unfavourable. Supraventricular arrhythmias and bradyarrhythmias were not adverse prognostic factors unlike ventricular arrhythmias, and here again the data are in agreement with the findings of Norris *et al.* Cardiac arrest, which in this case means ventricular fibrillation, was associated with a survival rate of 63 per cent at 3 years and 35 per cent at 5 years, conspicuously worse than for the series as a whole, while Norris and Mercer (1973) reported a 3-year survival of 58 per cent.

The two factors of increasing age and a previous history of angina pectoris were found to be of borderline significance in the present study where both the Health Insurance Programme Study of Frank *et al.* (1973) and the series of Norris *et al.* found them to be significant factors. The data also did not confirm Norris's finding of a significantly worse prognosis in anterior as opposed to inferior infarcts and transmural as opposed to intramural infarcts.

There is thus a large amount of agreement in published series regarding most of the factors which indicate a poor 5-year survival after myocardial infarction. These differ both from the risk factors associated with the development of signs of coronary disease and the factors relating to the outcome of an acute myocardial infarction. The present study has attempted to identify the most important of these factors and secondly (Fig. 2) to show how closely the long-term prognosis is linked to the number of these 6 factors identified as present when the patient leaves hospital after recovery from acute infarction.

References

Beard, O. W., Hipp, H. R., Robins, M., Taylor. J. S., Ebert, R. V., and Beran, L. G. (1960). Initial myocardial infarction among 503 veterans. *American Journal of Medicine,* **28,** 871–883.

Cox, D. R. (1970). *The Analysis of Binary Data,* pp. 87–91. Methuen, London.

Cutler, S. J., and Ederer, F. (1958). Maximum utilization of the life table method in analyzing survival. *Journal of Chronic Diseases,* **8,** 699–712.

Frank, C. W., Weinblatt, E., and Shapiro, S. (1973). Angina pectoris in men; prognostic significance of selected medical factors. *Circulation,* **47,** 509–517.

Honey, G. E., and Truelove, S. C. (1957). Prognostic factors in myocardial infarction. *Lancet,* **1,** 1155–1161.

Juergens, J. L., Edwards, J. E., Achor, R. W. P., and Burchell, H. B. (1960). Prognosis of patients surviving first clinically diagnosed myocardial infarction. *Archives of Internal Medicine,* **105,** 444–450.

Leren, P. (1970). The Oslo diet-heart study. *Circulation,* **42,** 935–942.

Norris, R. M., Caughey, D. E., Mercer, C. J., and Scott, P. J. (1974). Prognosis after myocardial infarction. Six year follow-up. *British Heart Journal,* **36,** 786–790.

Norris, R. M., and Mercer, C. J. (1973). Long-term prognosis following treatment in a coronary care unit. *Australian and New Zealand Journal of Medicine,* **3,** 31–37.

Pell, S., and D'Alonzo, C. A. (1964). Immediate mortality and five-year survival of employed men with a first myocardial infarction. *New England Journal of Medicine,* **270,** 915–922.

Zukel, W. J., Cohen, B. M., Mattingley, T. W., and Hrubec, Z. (1969). Survival following first diagnosis of coronary heart disease. *American Heart Journal,* **78,** 159–170.

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British Heart Journal, 1977, **39**, 1172–1178

Teesside coronary survey—fatality and comparative severity of patients treated at home, in the hospital ward, and in the coronary care unit after myocardial infarction

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An epidemiological survey of myocardial infarction in Teesside County Borough was completed between April 1972 and April 1973. Cases were notified and divided into those who had suffered a 'definite', 'possible', or 'not' myocardial infarction. Severity factors were measured in the 'definite' cases and the distribution of the various factors studied among home, ward, and coronary care unit treated cases. Increasing severity was found to be related to increased fatality. The fatality of patients treated at home was less than that of those treated in the ward or the coronary care unit. Those who survived to be treated at home were not less severe than those who survived in a comparable group to be treated in hospital using the objective criteria described in the assessment of severity. It is emphasised that the results must be interpreted with caution as other essentially subjective criteria not so easily measurable, but which might have been of considerable influence in the assessment of severity, were not measured in this study.

The Teesside Coronary Survey appeared to show that patients who had suffered a myocardial infarction and were treated at home fared better than those admitted to hospital (Colling *et al.*, 1976). A simple explanation for this might have been that there was a difference in severity between the groups of cases treated. It was essential, therefore, to try to measure severity in these patients. The size of the survey and the fact that many cases were treated at home presented difficulties and precluded using an index such as the Norris Index (Norris *et al.*, 1969) which includes certain physical signs and measurements such as radiological oedema. The Peel Index (Peel *et al.*, 1962) has been widely used in epidemiological work and appeared appropriate to this study.

Methods

This study is part of an epidemiological survey of coronary artery disease in Teesside County Borough (now part of Cleveland County), carried out in the year April 1972 to April 1973. Details of the organisation of the project have been discussed elsewhere (Colling *et al.*, 1976). The object was to study all episodes of myocardial infarction occurring within the Teesside County Borough whether these occurred at home or in hospital. The County Borough had a population of 396 230 and was, at the time of the survey, served by 150 general practitioners, 14 hospitals, and 2 coronary care units. The necessary information was obtained by direct contact with patients whenever possible, supplemented by information from their family doctors and the family itself. This information was obtained by 4 specially trained nurses who visited the patients at home, in the hospital ward, or in the coronary care unit, within 24 hours, at 72 hours, and at 28 days after the attack. In addition to completing a detailed form recording symptoms, certain signs, medical, and personal details, an electrocardiogram was recorded and blood samples were obtained for enzyme analysis at the time of the first two visits. Some of these measurements had been obtained by hospital staff in those patients admitted to hospital. Cases were classified using modified WHO criteria (World Health Organization, 1959) as having suffered a 'definite', 'possible', or 'not' myocardial infarction.

The severity index devised by Peel *et al.* (1962) was modified to incorporate the information that

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Table 1 *Modified peel index*

		Severity Score
Age and sex		
Men	*Women*	
< 55 years		0
55–59 years		1
60–64 years	< 65 years	2
> 65 years	> 65 years	3
Past history		
Previous myocardial infarct		6
Other cardiovascular disease, exertional dyspnoea		3
Angina only		1
No cardiovascular disease		0
Shock		
BP > 100mm Hg		0
BP < 100 mmHg		4
BP < 100 mmHg with cold extremities		7
Failure		
Not breathless		0
Breathless		4
Electrocardiogram		
Normal		0
Normal QRS (i.e. ST and T wave changes)		1
QR		3
QS or BBB		4
Rhythm		
Sinus		0
One or more of: Atrial fibrillation or flutter; paroxysmal atrial tachycardia; sinus tachycardia > 110 min; frequent ectopics; nodal rhythm; or block		4
Aspartate aminotransferase		
< 12 units (normal)		0
12 to 60 units		1
> 60 units		4

nurses had obtained and to include biochemical data (Table 1). The severity scores given to each of the factors in the modified index were derived from the original Peel Index which does not, however, include serum enzyme levels. Appropriate severity scores for the serum aspartate aminotransferase (SGOT) were derived from published reports relating fatality to aspartate aminotransferase levels (Chapman, 1971). The electrocardiographic criteria for infarction and analysis of rhythm changes were taken from the first electrocardiogram, and the aspartate aminotransferase level from the initial estimation either in hospital or at home. The scores obtained were related to fatality defined as death at or within 28 days of the incident.

The study of fatality in relation to severity was confined to patients who had been classified as having had a 'definite' myocardial infarction (a diagnostically well defined group) and had survived long enough to receive care and have the diagnostic investigations applied. Only one patient who was kept at home died between the time of notification and arrival of the nurse.

Results

The number of cases and corresponding fatality in each group is shown in Table 2. This paper examines the severity, distribution, and fatality of patients with a 'definite' myocardial infarction in group A. In 737 of these the place of treatment was known and their distribution and fatality rates are illustrated in Table 3. When the modified Peel Index was applied to these cases and the banded scores plotted against fatality rates the results are seen in Fig. 1. The regression line is significant $(P < 0{\cdot}01)$, indicating that severity as measured by the Peel Index is related to fatality. The distribution of the modified Peel scores by the three places of treatment is illustrated in Fig. 2. The difference in the percentage of patients in each score group treated at home, in the ward, and in the coronary care unit did not reach statistical significance.

The modified Peel Index did not, therefore, reveal any difference in severity between the patients in the three places of treatment but it is a relatively insensitive index, and in addition missing observations enabled it to be applied to only 590 cases. It was thought possible that the overall index might also mask the effect on fatality of an individual factor in the index. Each factor was, therefore,

Table 3 *Crude fatality for 'definite' myocardial infarct only*

	Home	*Ward*	*Coronary care unit*
Total cases	193	296	248
Fatality (%)	8·8	20·7	12·8

Table 2 *Classification of myocardial infarction*

Classification		*Criteria*	*No.*	*Deaths*
Definite myocardial infarction	(A)	Evolving injury current on electrocardiogram, *or typical* history with raised enzyme levels plus Q waves, ST changes, T wave changes, or bundle-branch block	751	115
	(B)	Postmortem evidence of myocardial infarct or occlusion	366	366
Possible myocardial infarction	(A)	A *typical* history of prolonged chest pain associated with non-diagnostic electrocardiogram, serum enzyme levels might be normal or raised	333	10
	(B)	Deaths *certified* as resulting from myocardial infarction	488	488
Not myocardial infarction		*Atypical* history with non-diagnostic electrocardiogram and normal serum enzymes; in other cases alternative diagnosis obvious after notification, or data insufficient to permit classification	833	0

examined independently in relation to fatality. The subsequent tables indicate that the number of missing observations for the individual factors were very few indeed—in all cases less than 5 per cent.

AGE AND SEX

As can be seen from Fig. 3, fatality tends to increase with age and there was no significant difference between the fatality rates for the two sexes. There was a significantly lower fatality, however, in patients who were under 65 years of age than in those who were 65 years of age and over ($P < 0 \cdot 001$).

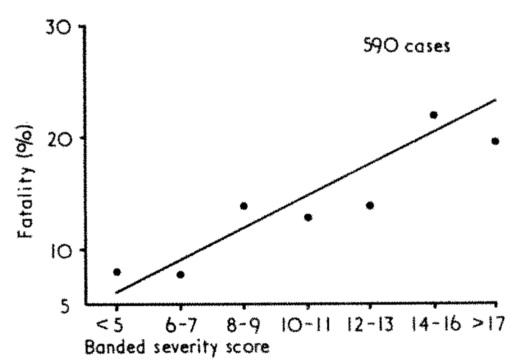

Fig. 1 *Severity score related to fatality.*

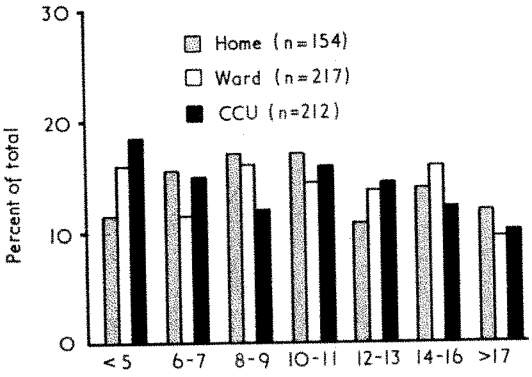

Fig. 2 *Severity score related to place of treatment: home, ward, and CCU in each severity band.*

Perhaps because of admission policy or some other selective factor, the group with the high fatality rates, i.e. those over the age of 65, did not go into the Coronary Care Units (Fig. 4). There were 43 per cent of patients over 65 years of age and 81 per cent of these went into the hospital ward or stayed at home. As far as age is concerned, therefore, the coronary care units appear to be treating the milder cases. The crude fatality rates were, therefore,

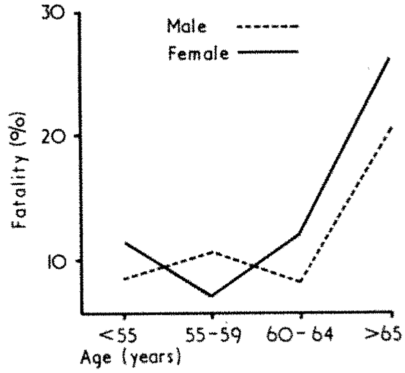

Fig. 3 *Fatality related to age and sex.*

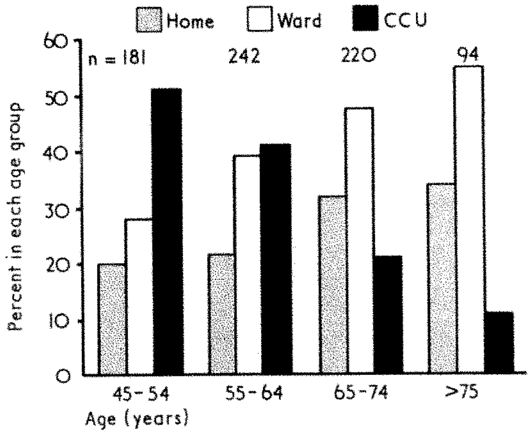

Fig. 4 *Age related to place of treatment: home, ward, and CCU.*

Table 4 *Age distribution and fatality by home, ward, and CCU: men*

Age (y)	*Home*			*Ward*			*CCU*		
	No.	*Deaths*	%	*No.*	*Deaths*	%	*No.*	*Deaths*	%
45–54	31	2	6·5	41	4	9·8	75	6	8·0
55–65	33	1	3·0	61	5	8·2	74	8	10·8
65–74	45	4	8·9	62	12	19·4	25	6	24·0
> 75	12	3	25·0	20	8	40·0	4	1	25·0
Standardised fatality %			7·3			14·1			14·6

Table 5 *Age distribution and fatality by home, ward, and CCU: women*

Age (y)	*Home* *No.*	*Deaths*	*%*	*Ward* *No.*	*Deaths*	*%*	*CCU* *No.*	*Deaths*	*%*
45–54	6	0	0	11	1	9·1	17	3	17·6
55–64	20	2	10·0	30	5	16·7	24	2	8·3
65–74	26	2	7·7	40	13	32·5	22	4	18·2
>75	20	3	15·0	31	13	42·0	7	2	28·6
Standardised fatality %			9·0			26·9			17·6

Table 6 *Fatality relating to past history*

Past history	*No.*	*Fatality %*
Nil	372	15·6
Angina	78	17·9
Other cardiovascular disease	80	15·0
Myocardial infarction	190	15·8
	720	

weighted appropriately so as to standardise the effect of age on fatality rates. The results for each sex are illustrated in Tables 4 and 5.

PAST HISTORY

When the fatality rates of cases with a past history of angina, other cardiovascular disease, or myocardial infarction were compared with those without such a past history, no statistical significance was found (Table 6). Furthermore, the distribution of past history by home, ward, and coronary care unit was found to be similar.

SHOCK

Peel and his colleagues did not define shock clearly and in this survey a definition of shock (warm or cold) was a systolic blood pressure of less than 100 mmHg. Of the 721 'definite' cases in which the measurements were obtained (96% of total cases), 8·7 per cent had such a blood pressure compared with 12 per cent in the Bristol series (Mather *et al.*, 1971). However, the fatality rates for those with a blood pressure level of more than 100 mmHg was 14·3 per cent and this did not differ significantly from those with a blood pressure of 100 mmHg or less (17·5%). The few cases with a low blood pressure (63) appeared to be equally distributed between the home, ward, and coronary care unit.

Table 7 *Fatality related to breathlessness*

	No.	*Fatality %*
Not breathless	541	13·3
Breathless	174	20·1
	715	

CARDIAC FAILURE

This was assessed by the presence or absence of breathlessness and was associated with a significantly increased fatality rate ($P < 0{\cdot}01$) (Table 7). Breathlessness was, however, related very significantly to increasing age ($P < 0{\cdot}001$) which was considered to be the more important variable in this context.

EXTENT OF INFARCTION ON ELECTROCARDIOGRAM

Fatality increased significantly with increasing electrocardiographic severity ($P < 0{\cdot}01$) (Table 8). The extent of the infarction on the electrocardiogram was unrelated to age and was evenly distributed between home, ward, and coronary care unit.

ARRHYTHMIAS

The presence of arrhythmias as listed in Table 1 and as assessed from the first electrocardiogram doubled fatality (21·5% as compared to 10·4%) ($P < 0{\cdot}01$). Approximately 30 per cent of patients had some form of arrhythmias on the first electrocardiogram. Of home cases 26 per cent, of ward cases 32·5 per cent, and of coronary care unit cases 32·5 per cent had abnormal rhythms, differences that

Table 8 *Fatality related to extent of infarction*

Electrocardiographic changes	*No.*	*Fatality %*
Normal	157	8·9
Intramural	196	11·2
QR	157	21·0
QS: BBB	241	19·1
	751	

Table 9 *Fatality related to aspartate aminotransferase level*

Aspartate aminotransferase IU/l	*No.*	*Fatality %*
<12	143	9·1
12–60	399	12·7
>60	170	23·7
	712	

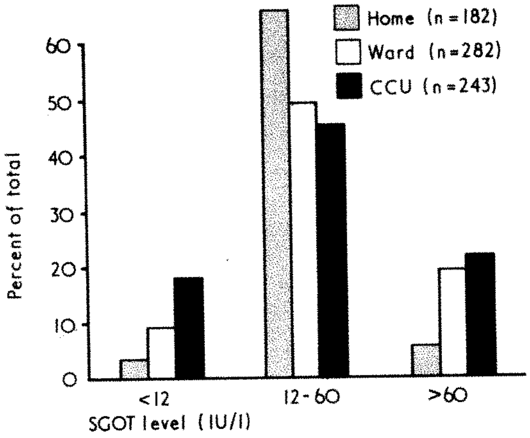

Fig. 5 *Aspartate aminotransferase level related to place of treatment: home, ward, and CCU.*

were not statistically significant. The incidence of arrhythmias was independent of age.

ASPARTATE AMINOTRANSFERASE LEVEL

The normal level in this study was < 12 IU units per litre. Fatality increased overall with higher aspartate aminotransferase levels (Table 9). The differences were significant only between groups of patients who had levels of less than 60 and those with levels of greater than 60 units per litre ($P < 0{\cdot}001$). The influence of the aspartate aminotransferase on fatality was found to be independent of age, sex, and the extent of infarction as measured on the electrocardiogram. The distribution of the aspartate aminotransferase levels between the home, the ward, and the coronary care unit was not even (Fig. 5). Thus 80 per cent of cases with levels of greater than 60 units per litre, i.e. those cases with the higher fatality rates, tended to go into the ward or into the coronary care unit. There were 170 such cases (23·9% of the total). Because of the unequal distribution, the crude fatality rates were standardised for this aspartate aminotransferase factor and such standardisation did not materially alter the crude fatality rates (Tables 10, 3).

Discussion

Two methods have been used to assess the severity of cases who had suffered a 'definite' myocardial infarction and survived sufficiently long to come under medical care. The first involved the use of an index of severity based on that of Peel and his colleagues. The severity scores for the cases in the three places of treatment were similar. However, the index is a relatively crude indicator of severity. In the second method the individual severity factors were related to fatality, and it is apparent that the weightings given by Peel to certain of the factors are incorrect in the Teesside context. Again from this second part of the analysis it seems that for most of the factors increasing severity was associated with increasing fatality. The two exceptions are a previous history of myocardial infarction, contrary to the experience of Peel and his colleagues (1962), and the presence of shock, which is contrary to the experience of other observers, including Mather *et al.* (1971). A possible explanation for this latter finding is that blood pressures taken at the time of hospital admission were not necessarily comparable with those taken by the nurses when they visited the patient at home.

The only two factors in the index with a significant effect on fatality, which were unequally distributed between the home, the ward, and the coronary care unit, were age (over 65 years) and aspartate aminotransferase (greater than 60 units per litre). The latter variable was present in a relatively small number of patients and it is, therefore, not surprising that it was only standardisation for age that made an appreciable difference to the crude fatality rates obtained (Tables 4, 5).

Clearly then cases with a 'definite' myocardial infarction who survived to be treated did better at home than in hospital regardless of whether hospital treatment was in the ward or in the coronary care unit. Women treated in the ward appeared to do particularly badly. It is of interest to see the effects of three of the risk factors studied, age, aspartate aminotransferase level, and extent of infarction on the electrocardiogram, on fatality rates in the three

Table 10 *Aspartate aminotransferase distribution and fatality by home, ward, and CCU*

Aspartate aminotransferase (units)	*Home* *No.*	*Deaths*	*%*	*Ward* *No.*	*Deaths*	*%*	*CCU* *No.*	*Deaths*	*%*
< 12	36	3	8·3	48	5	10·5	59	5	8·5
12–60	120	9	7·5	162	30	18·5	117	13	11·1
> 60	26	2	7·7	74	23	31·0	70	15	21·4
Standardised fatility			7·7			19·9			13·1

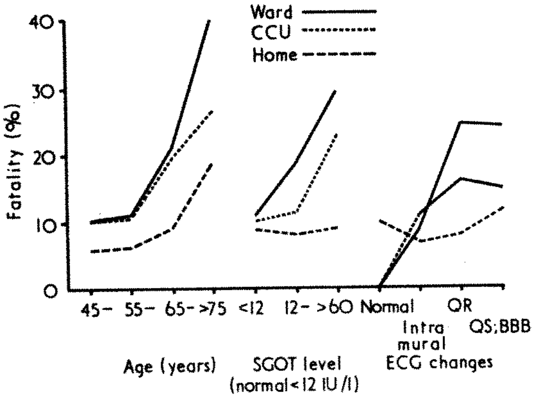

Fig. 6 *Fatality related to age, aspartate aminotransferase, and electrocardiogram at places of treatment.*

places of treatment (Fig. 6). For all degrees of severity patients did better at home.

Important in the interpretation of the data is the fact that low fatality rates at home might possibly indicate that some home treated cases had not been notified to the survey. It has been emphasised elsewhere (Colling *et al.*, 1976) that many precautions were taken to ensure complete notification. This included exhaustive consultation with hospitals and general practitioners, the registrar of births, deaths and marriages, the coroner, the Teesside Medical Relief Service, the Bed Bureau, and industrial medical officers. In addition weekly lists of deaths relating to the Teesside population sent automatically to the Health Department were studied and details of relevant cases were extracted by the team's staff. None the less it was important to be sure that general practitioners had notified home deaths. A retrospective analysis was initiated to try and elucidate this matter further. All cases certified as having died from myocardial infarction either on clinical or postmortem evidence, who were visited by the general practitioner within 4 days before death during the first 6 months of the survey were analysed. From this study it was calculated that over the year approximately 10 to 12 home treated deaths may not have been notified. These numbers would alter the fatality rates but not to the point of removing the advantage for the home treated cases, especially after standardising for the effect of age on fatality rates.

A discussion on this subject should comment on the delay experienced by the different groups of cases before they came under medical care. Different delays will influence observed fatality rates because of the high fatality known to complicate myocardial infarction in the first two hours after onset. This was confirmed by the Teesside survey (Colling *et al.*, 1976).

In the Teesside survey an important difference between the home and the hospital group was that for home cases the median interval between the onset of the attack and the arrival of the general practitioner was approximately twice as long as for those admitted to hospital (2·63 hours as compared to 1·3 hours). However, the delay in moving patients to hospital increased the median time of patients coming under care in hospital to just under 3 hours, i.e. similar to the delay at home. During this time some patients died while being transferred to hospital but these are excluded from the hospital deaths. Comparison of the fatality rates between the home and the hospital group of cases is, therefore, valid providing the cases can be shown to be of similar severity.

Though the two groups are, therefore, comparable it is not possible to be certain that the first clinical assessment was made at a similar time within the 24-hour interval after onset in the home and hospital groups. Certain of the objective criteria which have been applied as measurements of severity—age, sex, and past history will not be affected by such differences, but this is not necessarily the case with the other variables (see Table 1). It will be recalled, however, that these measurements were repeated at 72 hours. When they were analysed in the manner already discussed for the first measurements, i.e. in terms of fatality and between the three treatment venues, the results were similar to those obtained using the first measurements.

It could be argued that the shorter time interval of general practitioner attendance for hospital cases than home cases relates in some way to severity. The main cause of delay in this, as in other studies, was 'patient delay' (Colling *et al.*, 1976). It is possible that the more severe episodes resulted in a shorter 'patient delay' interval and that the sense of urgency was also transmitted to the general practitioner, who attended earlier and tended to admit these cases. This may be an important severity factor which was not measured because it cannot be measured. Indeed it must be admitted that there may be many other factors making up 'severity' which cannot be measured. How important these might be in relation to the objective criteria which have been described and related to fatality in this study can only remain speculative.

It must be emphasised that apart from any reservations about the validity of interpreting severity factors, this study is not intended to resolve the debate as to whether home or hospital is the best place to treat patients with a myocardial infarction. It does indicate that for those who have survived the 3-hour interval from apparent onset, the coronary care unit may have little to offer and this has important implications because it is a reasonable supposition that similar delays exist before admission in many hospitals which otherwise run efficient coronary care units. The study we feel indicates more than ever the need to make coronary care unit facilities available to cases earlier so that their potential impact on fatality can be assessed. We have, in fact, established such facilities on Teesside, and a report of their efficacy will be the subject of a further communication.

Conclusion

The comparative fatality figures presented here suggest that for those patients admitted to hospital coronary care units were of benefit, especially if the patient was a woman. There appears, however, to be little evidence that coronary care units benefited the patients who had survived at home for the median interval (3 hours) before they came under the care of the general practitioner. The data presented suggest that the cases treated at home were of similar severity to those treated in hospital as assessed by the objective criteria which have been described and applied to them, even though the reservations which are associated with this exercise are emphasised.

We are grateful to all the nurses and doctors on Teesside who contributed by collecting information for this survey and to their secretaries who notified the cases. We would especially like to thank Sisters E. Young, C. Kirby, C. Smith, and Staff Nurse C. Wylie who worked more than full-time on the project, and Mr. O. Downing who co-ordinated the routine work so effectively; Mrs. S. Hyde and Mr. M. Byrne who, with Mrs. J. Garlick, analysed the data and prepared a preliminary report. Mr. K. Coates, Research Officer, other members of the Teesside Health Department, and the Statistical Section of the Northern Regional Health Authority gave invaluable assistance. We are also grateful to Dr. E. W. Walton, the late Dr. S. Ray, and staff for their pathology services; to Mr. F. E. Harper, Biochemist; to Mr. M. Sheffield, coroner; and Mr. E. Gifford, chief ambulance officer and many others who helped in vital ways; and also to Professor J. N. Morris, Professor D. G. Julian, Dr. M. Oliver, and Dr. H. Tunstall Pedoe, who gave valuable help in the planning stages.

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References

Chapman, B. L. (1971). Correlation of mortality rate and serum enzymes in myocardial infarction. *British Heart Journal*, **33**, 643–646.

Colling, A., Dellipiani, A. W., Donaldson, R. J., and MacCormack, P. (1976). Teesside coronary survey. *British Medical Journal*, **2**, 1169–1172.

Mather, H. G., Pearson, N. G., Read, K. L. Q., Shaw, D. B., Steed, G. R., Thorne, M. G., Jones, S., Guerrier, C. J., Eraut, C. D., McHugh, P. M., Chowdhury, N. R., Jafary, M. H., and Wallace, T. J. (1971). Acute myocardial infarction: home and hospital treatment. *British Medical Journal*, **3**, 334–338.

Norris, R. M., Brandt, P. W. T., Caughey, D. E., Lee, A. J., and Scott, P. J. (1969). A new coronary prognostic index. *Lancet*, **1**, 274–278.

Peel, A. A. F., Semple, T., Wang, I., Lancester, W. M., and Dall, J. L. G. (1962). A coronary prognostic index for grading the severity of infarction. *British Heart Journal*, **24**, 745–760.

World Health Organization (1959). Hypertension and coronary heart disease: classification and criteria for epidemiological studies. *World Health Organization. Technical Report Series*, No. 168.

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Multiple risk prediction of myocardial infarction in women as compared with men

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A study was undertaken to determine whether women who suffer a myocardial infarction in spite of the low frequency in this sex, are more heavily burdened by coronary risk factors than other women and men of similar age. Data were obtained from two random population samples of 855 men and 396 women aged 50 years and compared with all men (n=160) and women (n=60) suffering non-fatal primary myocardial infarcts during 1968 to 1970 and 1968 to 1974, respectively.

Women with infarction had higher blood pressure values, higher triglyceride values, and smoked considerably more than women in the general population. The cholesterol values were not significantly higher in the women with infarction.

The multivariate risk, based on cholesterol level, systolic blood pressure, and smoking habits, in the women with infarction was very similar to that in the men with myocardial infarction. There was no major difference in risk between pre- and postmenopausal women. A higher prevalence of diabetes mellitus in the women with infarction compared with the general population could not explain their increased risk for myocardial infarction. Thus, other factors must be operating in addition to the traditional risk factors.

The incidence of myocardial infarction is higher in men than in women. From a Myocardial Infarction Register, we found the incidence to be about 6 times higher in men than in women in the age group 45 to 54 years (Elmfeldt *et al.*, 1975a). The prevalence of angina pectoris as determined by a questionnaire was, however, similar in the two sexes (Bengtsson, 1969). Because of the low incidence of myocardial infarction in women, few population studies have been able to give an indication of prospective risk factors for this disease in women. In most communities, the only way of finding risk factors in women would be to perform well-designed case control studies.

In the Framingham study (Kannel and Castelli, 1972), it was found that the same risk factors seem to operate in women as in men. It has been found that the mean age at the menopause was somewhat lower among women with myocardial infarction than among women in general population samples of similar age (Bengtsson, 1973; Kannel *et al.*, 1975). In a report on myocardial infarction women several of the patients were still menstruating (Bengtsson, 1973), suggesting the protective effect of the female hormone pattern can be nullified. A question of relevance in this connection is whether those women who suffer a myocardial infarct, but who are still menstruating, are more heavily burdened by coronary risk factors than other women and men of similar age.

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The present paper reports some data concerning multivariate risk prediction based on serum cholesterol level, systolic blood pressure, and smoking habits, with the aim of comparing the risk factor profile in the male and female population and in men and women who had suffered a myocardial infarct. Prospective data from a population study in men were available (Wilhelmsen *et al.*, 1973).

Study population and methods

Since 1 January 1968, all cases of acute myocardial infarction occurring in the population of Göteborg in certain age groups have been registered by a special organisation (Elmfeldt *et al.*, 1975a). The register includes 90 per cent of all surviving diagnosed cases of myocardial infarction in the city. Patients discharged from hospital alive are systematically followed at a special clinic—The Post-MI

Clinic (Wilhelmsen, 1969; Elmfeldt *et al.*, 1975b). During the years 1968 to 1970, 160 men aged 45 to 54 years (mean age 50·3 years) had survived a primary myocardial infarct. Data from these men have been reported earlier (Elmfeldt *et al.*, 1976a, b). Because of the lower incidence of myocardial infarction in women we collected female cases for a longer period from 1968 to 1974. A total of 60 women surviving a primary myocardial infarct in the age group 45 to 54 years (mean age 50·6 years) were registered during this time.

It has been shown that serum cholesterol and blood pressure as well as smoking habits change with myocardial infarction, but studies of a population sample examined before as well as after myocardial infarct have enabled us to allow for the effect of these changes (unpublished observations). Thus, an estimate of the probability of suffering a myocardial infarct has been made retrospectively for the patients—both men and women—in the present study. This was done by means of a multiple risk function developed from a multivariate logistic analysis by Wilhelmsen *et al.* (1973) modified through an isotonic regression technique (Barlow *et al.*, 1972) adopted by us for computer analysis. This function gives the estimated probability of a 50-year-old man suffering a myocardial infarct during 10 years of follow-up based on three factors, serum cholesterol, systolic blood pressure, and tobacco smoking. The estimated probabilty will be referred to below as 'the risk'. For ease in practical use a nomogram of the risk function was constructed (Fig. 1).

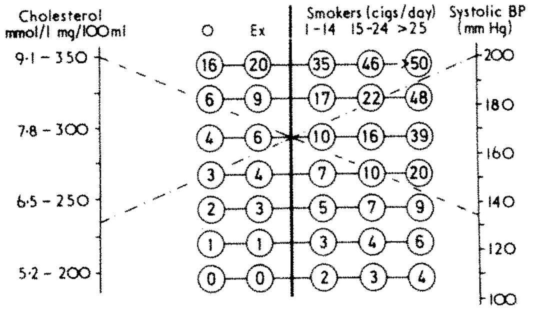

Fig. 1 *Nomogram for determination of estimated probability of a 50-year-old man without clinical signs of coronary heart disease suffering myocardial infarction before the age of 60 years. The numbers within circles denote the number of men aged 50 out of 100 who develop myocardial infarction during 10 years' follow-up.*
By connecting the cholesterol value and systolic blood pressure value of the subject, the vertical line will be crossed near a horizontal line; the risk for the appropriate smoking habit can be found in the circle in the relevant column.

Patients were asked about one week after the myocardial infarct about their smoking habits. According to earlier reports, serum cholesterol had usually returned to preinfarction levels about 3 months after infarction (Tibblin and Cramér, 1963; Cotton, 1970; Fyfe *et al.*, 1971). As we had found the same results in patients controlled by us we used the values from the check-up 3 months after the myocardial infarct (unpublished observations). Blood pressure has been shown to fall during an infarct and the reduction of systolic blood pressure was estimated to be 15 mmHg on average in a special study in which blood pressure values were available before as well as after the myocardial infarct. The distribution of blood pressure decrease was approximately symmetrical, and the decrease was not related to the initial blood pressure level (Wilhelmsen *et al.*, to be published). The values after infarction were, therefore, increased by this amount when calculating the risk.

Of the 160 male patients and 60 female patients discharged alive from hospital, 154 and 53, respectively, were alive 3 months after the acute infarct. Complete data were available for 150 men and 52 women and the risk of these patients was calculated in accordance with the risk function.

For comparison between the male myocardial infarct patients and the general male population, we used data for 50-year-old men from the study of men born in 1913 (Tibblin, 1965, 1967). The participation rate in that study was 88 per cent. Of the 855 men who were examined at entry in 1963, 834 were free of clinical myocardial infarct. These men have been followed for 10 years.

Data from a random population sample of 50-year-old women also living in Göteborg were obtained from the study by Bengtsson (1973). From 398 participants all free of clinical myocardial infarct at the first examination in 1968 data for this analysis were available for 396 women. The participation rate in the study of women was 91 per cent. These women have been followed up for 7 years.

Data from another population sample comprising 387 women aged 52 years in 1974 and examined with the same methods were available for analysis of any time trend between 1968 and 1974 in smoking habits, blood pressure, or serum cholesterol.

Both the patients and the population samples were drawn from the population of the same city and were investigated and interviewed according to standardised methods used during the entire period, by the same team. The methods have been described in detail previously and careful checks of their comparability have been performed (Bengtsson, 1973; Elmfeldt *et al.*, 1975a, b).

Table 1 *Blood pressure, serum cholesterol, serum triglycerides, and smoking habits in men, and pre- and postmenopausal women in the population samples and in those with myocardial infarction*

	Population samples age 50 years				*Myocardial infarct patients from MI-clinic age 45 to 54 years*			
	Men	*Women*			*Men 1968-70*	*Women 1968–74*		
		Total	*Premenopause*	*Postmenopause*		*Total*	*Premenopause*	*Postmenopause*
Number	855	384	185	148	150	52	21	31
Systolic blood pressure (mmHg)								
Mean	138	138	140	135	139	148	148	148
SD	21	21	22	21	23	22	21	23
Serum cholesterol (mmol/l)								
Mean	6·4	6·9	6·6	7·2	7·2	7·1	6·7	7·3
SD	1·1	1·1	0·9	1·2	1·4	1·5	1·2	1·6
Triglycerides (mmol/l)								
Mean	1·3	1·0	0·9	1·1	1·8	1·8	1·8	1·8
SD	0·8	0·6	0·5	0·7	1·0	0·9	0·8	0·9
Never smoked (%)	24	56	66	47	4	23	15	28
Ex-smoker (%)	20	7	7	7	8	7	5	8
Smokers (%)								
1-14 g/day	35	30	23	36	31	29	15	36
≥15 g/day	21	7	4	10	57	41	65	28

Results

Table 1 gives data for blood pressure, serum cholesterol, serum triglycerides, and smoking habits in men and women from the population samples and patients with myocardial infarction.

Table 2 gives a comparison between the two female population samples (age 50 and 52 years, respectively) examined in 1968 and 1974. Lower values for systolic blood pressure ($P<0{\cdot}01$), and higher values for cholesterol ($P<0{\cdot}05$) and triglycerides ($P<0{\cdot}01$) were found among the 52-year-old women, who also smoked more ($P<0{\cdot}01$).

The data for women in Table 1 are given for premenopausal and postmenopausal women, respectively. It is to be noted that the blood pressure values were *not* adjusted (increased by 15 mmHg) for the myocardial infarction patients in this table.

Table 2 *Values from the two female population samples*

	1968 50 years (n = 384)	*1974 52 years (n = 387)*
Systolic blood pressure (mmHg)		
Mean	138	133
SD	21	20
Serum cholesterol (mmol/l)		
Mean	6·9	7·1
SD	1·1	1·2
Triglycerides (mmol/l)		
Mean	1·0	1·3
SD	0·6	0·5
Never smoked (%)	56	50
Ex-smoker (%)	7	10
Smokers (%)		
1–14 g/day	30	24
≥15 g/day	7	16

The blood pressure values were higher for both pre- and postmenopausal women with infarction compared with women from the general population ($P<0{\cdot}01$). Premenopausal women in the population sample had higher blood pressures than postmenopausal women ($P<0{\cdot}05$). Men with infarction had similar blood pressure values to men from the general population ($P>0{\cdot}05$), but it should be borne in mind that the myocardial infarct had decreased the mean value by about 15 mmHg (after correction $P<0{\cdot}01$).

There were small differences between women with infarction and women from the general population with respect to cholesterol values ($P>0{\cdot}10$). For the population sample of women a pronounced difference in mean values was found for women before and after the menopause ($P<0{\cdot}01$), and a similar but non-significant difference was found for the women with infarction ($P>0{\cdot}05$). However, there was still no difference between women with infarction and the general population when allowance was made for the effect of menopause. For men the expected difference in cholesterol values between men with infarction and men in the general population was found.

There was a difference in triglyceride values between women with infarction and women from the general population ($P<0{\cdot}01$). The triglyceride values were higher in the postmenopausal than in the premenopausal women in the general population ($P<0{\cdot}01$), but for the women with infarction no such tendency was found. Thus, the difference was somewhat greater in the premenopausal than in the postmenopausal women. The men with infarction also had higher triglycerides than the men from the general population ($P<0{\cdot}01$).

The correlation coefficients between cholesterol and triglycerides were 0·33 to 0·38 for both men and women in the population samples as well as in the infarct groups. There were no differences in correlation coefficients if the women were divided with respect to menopause.

The women with infarction were much more often smokers than women in the general population ($P < 0{\cdot}01$). An especially pronounced difference compared with the general population was found for premenopausal women with infarction among whom 65 per cent smoked 15 cigarettes a day or more as compared with 4 per cent in the general population. The postmenopausal women in the general population smoked more ($P < 0{\cdot}01$) than the premenopausal women.

If the women with infarction are compared with the population sample of women examined in 1974 (aged 52 years) there is still a difference in systolic blood pressure ($P < 0{\cdot}01$), no difference in cholesterol values, and still a pronounced difference in triglycerides ($P < 0{\cdot}01$). Even though the women examined in 1974 smoked more than those examined in 1968, there is still a pronounced difference ($P < 0{\cdot}01$).

Fig. 2 shows the distribution of risk of myocardial infarct according to the multiple risk function for the random population sample of men and for the 150 men with primary myocardial infarct, as well as the same distributions for women in the female population sample and the 52 women with primary myocardial infarct (blood pressure values now adjusted by 15 mmHg). The distributions of risk in the male and female *population samples* were similar. Thus, 89 per cent of both men and women had a predicted risk of 0·10 or less, and 2·6 per cent of the men and 2·5 per cent of the women had a risk of 0·20 or higher.

When comparing *men and women with myocardial infarction* it appears that the distributions with respect to risk also are very similar (Fig. 2); 35 per cent of the men and 40 per cent of the women with myocardial infarct had a predicted risk of 0·10 or less.

The number of men and women in the *population samples* who suffered a myocardial infarct during 10 years' and 7 years' follow-up, respectively, is shown in Table 3. The numbers are given in relation to classes of multiple risk. As the prediction formula was based on the incidence of myocardial infarction in the sample of men, it is self evident that the incidence must increase considerably with increasing values for estimated risk among the men, but there are evidently some men who suffered a myocardial infarct in spite of low risk as judged by cholesterol values, blood pressure values, and smoking habits. Of the 26 non-fatal myocardial infarct cases 18 (69%) and of the 18 fatal cases 9 (50%) had an estimated risk of 0·10 or less. Not a single woman in the population sample suffered a myocardial infarct during the 7 years' follow-up.

As seen in Table 4, 21 of the 52 women with myocardial infarction (all aged 45 to 54 years) were premenopausal. The mean ages of the premenopausal and postmenopausal women were 48·4 and 51·9 years, respectively. (Of the 31 postmenopausal

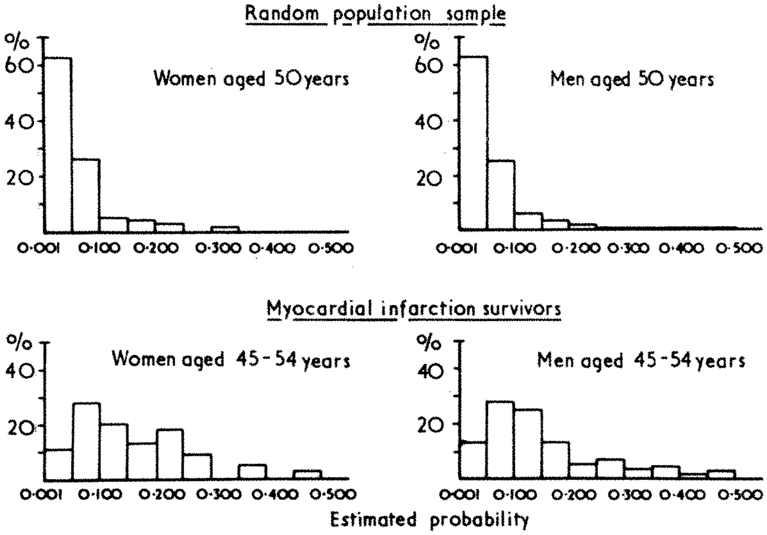

Fig. 2 *Estimated probability of suffering a myocardial infarct according to a multiple logistic function in a random sample of men aged 50 years (top right), men (45-54 years old) who have survived a myocardial infarct (bottom right) compared with a random sample of women aged 50 years (top left) and women (45-54 years) who have survived a myocardial infarct (bottom left).*

women, 3 had their menopause prematurely as a result of operations.) The median risk in premenopausal women was 0·13 and in the postmenopausal women 0·11. Of the 52 myocardial infarct women 16 were between 45 and 49 years; 11 of these were premenopausal and their median risk was the same as for the postmenopausal women in this age group. Among postmenopausal women there was no tendency towards a shorter time interval between menopause and acute myocardial infarction in women with the highest risk.

As mentioned above, cholesterol was not found to be associated with myocardial infarction in the women. Triglycerides were, however, higher in women with myocardial infarction. The possibility that women with infarction and low multiple risk had higher triglycerides than women with infarction and high multiple risk was examined but this was not found to be so. There was a pronounced increase in triglycerides with increasing multiple risk, and this is because of positive bivariate correlations between triglycerides and cholesterol ($r=0·38$), blood pressure ($r=0·10$), and smoking ($r=0·16$) in the women with infarction.

Six women had diabetes mellitus detected by glycosuria and 5 of these were between 50 and 54 years. The median risk in these 6 women was 0·10.

Discussion

It is difficult to assess the importance of risk factors which occur infrequently in the population, just as it is difficult to come to any conclusions concerning risk factors if the incidence of a disease is low. The former is a problem when, for example, diabetes is studied. In several prospective population studies diabetes has not been detected as a significant risk factor because manifest diabetes has a prevalence of only around 1 per cent in middle-aged men and women. By comparing patients who have already suffered a myocardial infarct with the general population it has, however, been possible to show the importance of diabetes as a risk factor in women and men in the Swedish population (Bengtsson, 1973; Elmfeldt *et al.*, 1976a, c). It has not been possible to assess the risk factors in the prospective population study of women during 7 years' follow-up since there have as yet been no episodes of myocardial infarction.

The methods used in this study have made it possible to examine the risk characteristics of Swedish women with myocardial infarction. It must, however, be stressed that a certain bias might have been introduced as the study only included non-fatal cases of myocardial infarction. That there

Table 3 *Number of men and women suffering a myocardial infarct (MI) in relation to multiple risk prediction*

Multiple risk	*Population samples age 50 years*					*MI patients from MI clinic age 45 to 54 years*	
	Men Total	*MI in 10 years' follow-up*		*Women Total*	*MI in 7 years' follow-up*	*Men registered 1968–1970*	*Women registered 1968–1974*
		Non-fatal	*Fatal*				
0·001–0·100	740	18	9	354	0	53	21
0·101–0·200	72	4	7	32	0	58	15
0·201–0·300	12	1	0	6	0	18	12
0·301–0·400	7	2	1	4	0	12	3
0·401–	3	1	1	0	0	9	1
Total	834	26	18	396	0	150	52

Table 4 *Multiple risk, median age, and triglycerides for pre- and postmenopausal women with myocardial infarction (MI)*

Multiple risk	*Premenopausal women*				*Postmenopausal women*				
	No.	*Median age*	*Triglycerides (mmol/l)*		*No.*	*Median age*	*MI years after menopause*	*Triglycerides (mmol/l)*	
			Mean	*SD*				*Mean*	*SD*
0·001–0·100	7	47	1·3	0·4	14	53	3	1·5	1·0
0·101–0·200	8	48	2·0	0·9	7	54	7	1·7	0·6
0·201–0·300	6	49	2·1	0·9	6	53	5	2·0	0·9
0·301–0·400	0	—	—	—	3	51	3	2·3	1·1
0·401–	0	—	—	—	1	52	5	2·5	
Total	21				31				

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may be differences in risk factor profiles between non-fatal and fatal myocardial infarction sufferers has been discussed in previous papers (Tibblin *et al.*, 1975; Elmfeldt *et al.*, 1976a, b, c). In a previous analysis it was found that hypertension, high triglycerides, smoking, and diabetes mellitus were more common among the women with myocardial infarction than among the general population (Bengtsson, 1973). The prevalence of diabetes mellitus among the women with myocardial infarction—15 per cent—was higher than the figure for diabetes among men with myocardial infarction —7 per cent. In the population samples diabetes was slightly more prevalent among women than men—1·3 and 0·8 per cent, respectively, but the difference is not statistically significant.

It seems reasonable to assume that at least some of the factors which are related to the differences between the sexes are connected with the precipitation of myocardial infarction and not the atherosclerotic process as such. It is evident from Table 3 and Fig. 2 that the protective effect of female sex is active irrespective of the multiple risk based upon the levels of blood pressure, serum cholesterol, and smoking habits.

The present analysis aimed at testing whether women, who had suffered a myocardial infarct despite the overall low incidence of this disease in middle-aged women, were more heavily burdened by the risk factors hypercholesterolaemia, hypertension, and smoking than are men with myocardial infarction.

We found, however, similar distributions of these risk factors in myocardial infarct patients in the two sexes and in general between pre- and postmenopausal women, which speaks against this hypothesis.

As in the Framingham study, it was found that serum cholesterol was higher in postmenopausal than in premenopausal women (Hjortland *et al.*, 1976). The present results indicate that high serum cholesterol is not such a strong risk factor for (non-fatal) myocardial infarction in women as in men. High triglycerides are apparently more common in infarct women. This finding is puzzling and difficult to explain in view of the fairly strong correlation between cholesterol and triglycerides in women and in men. The present results suggest that a high triglyceride level is an independent risk factor for myocardial infarction in women as opposed to the finding in men (Wilhelmsen *et al.*, 1973), but because of the lack of prospective data in women it cannot be proved by this study.

As only 6 women with myocardial infarct had diabetes, the higher prevalence of diabetes among women than among men with myocardial infarct can only partly explain why the influence of the female sex could not protect these particular women from myocardial infarction. Even though there were also some differences with respect to mental stress, certain personality traits, and physical inactivity between women with myocardial infarcts and the general population of women (Bengtsson, 1973), we cannot see that these differences can 'explain' why the women suffered myocardial infarction. Thus, we conclude from the present study that some other factor or factors must be responsible.

It is evident that there are as yet unidentified factors which are important for premature myocardial infarction. In this context it is interesting to compare the present findings with those of Keys (1972) who found that there must be some unknown risk factor or factors which explain the higher rate of myocardial infarction among American as compared with European men. We can only hypothesise about the possible mechanisms of such factors. Thus, they may have to do with the lipid metabolism of the vessel wall, the coagulation system, or even with the sensitivity of the myocardium to hypoxia or its tendency to react with catecholamine release. Wolinsky (1973) has shown experimentally that the vessel wall may react differently in male and female animals. If there are similar sex differences (brought about by oestrogens or androgens) with respect to the sensitivity of the myocardium in humans, they are not known at present, but are worthy of investigation.

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References

Barlow, R. E., Bartholomew, D. J., Bremner, J. M., and Brunk, H. D. (1972). *Statistical Inference Under Order Restrictions*. John Wiley, New York.

Bengtsson, C. (1969). The women study 1968–1969. *Pehr Dubb Journal (Göteborg)*, **4**, 4, 14–19.

Bengtsson, C. (1973). Ischaemic heart disease in women. *Acta Medica Scandinavica*, Suppl. 549.

Cotton, S. G. (1970). Plasma cholesterol after myocardial infarction. *Postgraduate Medical Journal*, **46**, 551–552.

Elmfeldt, D., Vedin, J. A., Wilhelmsson, C., Tibblin, G., and Wilhelmsen, L. (1976a). Morbidity in representative male survivors of myocardial infarction compared to representative population samples. *Journal of Chronic Diseases*, **29**, 221–231.

Elmfeldt, D., Wilhelmsen, L., Tibblin, G., Vedin, J. A., Wilhelmsson, C., and Bengtsson, C. (1975a). Registration of myocardial infarction in the city of Göteborg, Sweden. *Journal of Chronic Diseases*, **28**, 173–186.

Elmfeldt, D., Wilhelmsen, L., Tibblin, G., Vedin, J. A., Wilhelmsson, C., and Bengtsson, C. (1975b). A post-myocardial infarction clinic in Göteborg, Sweden. *Acta Medica Scandinavica*, **197**, 497–502.

Elmfeldt, D., Wilhelmsson, C., Vedin, J. A., Tibblin, G., and Wilhelmsen, L. (1976b). Characteristics of representative male survivors of myocardial infarction compared with representative population samples. *Acta Medica Scandinavica,* **199,** 387–398.

Elmfeldt, D., Wilhelmsen, L., Wedel, H., Vedin, A., Wilhelmsson, C., and Tibblin, G. (1976c). Primary risk factors in patients with myocardial infarction. *American Heart Journal,* **91,** 412–419.

Fyfe, T., Baxter, R. H., Cochran, K. M., and Booth, E. M. (1971). Plasma-lipid changes after myocardial infarction. *Lancet,* **2,** 997–1001.

Hjortland, M. C., McNamara, P. M., and Kannel, W. B. (1976). Some atherogenic concomitants of menopause: the Framingham study. *American Journal of Epidemiology,* **103,** 304–311.

Kannel, W. B., and Castelli, W. P. (1972). The Framingham study of coronary disease in women. *Medical Times (New York),* **100,** 173–195.

Kannel, W. B., Hjortland, M., and McNamara, P. (1975). Menopause and risk of cardiovascular disease: the Framingham study. Abstract of *Conference on CVD Epidemiology, Tampa, Florida, 10-11 March.*

Keys, A. (1972). Predicting coronary heart disease. In *Preventive Cardiology,* pp. 21–31. Ed. by G. Tibblin, A. Keys, and L. Werkö. John Wiley, New York.

Tibblin, G. (1965). A population study of 50-year-old men. An analysis of the non-participation group. *Acta Medica Scandinavica,* **178,** 453–459.

Tibblin, G. (1967). High blood pressure in men aged 50—a population study of men born in 1913. *Acta Medica Scandinavica,* Suppl. 470.

Tibblin, G., and Cramér, K. (1963). Serum lipids during the course of an acute myocardial infarction and one year afterwards. *Acta Medica Scandinavica,* **174,** 451–455.

Tibblin, G., Wilhelmsen, L., and Werkö, L. (1975). Risk factors for myocardial infarction and death due to ischemic heart disease and other causes. *American Journal of Cardiology,* **35,** 514–522.

Wilhelmsen, L. (1969). The myocardial infarction clinic in Göteborg—organization and preliminary results. *Pehr Dubb Journal,* **4,** 43–54.

Wilhelmsen, L., Wedel, H., and Tibblin, G. (1973). Multivariate analysis of risk factors for coronary heart disease. *Circulation,* **48,** 950–958.

Wolinsky, H. (1973). Comparative effects of castration and antiandrogen treatment on the aortas of hypertensive and normotensive male rats. *Circulation Research,* **33,** 183–189.

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Loss of electrically active myocardium during anterior infarction in man[1]

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A method has been developed of praecordial mapping of changes in R/S ratio and the appearance of Q waves in acute myocardial infarction. Observation of the serial changes in R and Q waves in 40 patients with uncomplicated anterior infarction shows that the loss of electrically active myocardium occurs within 6 hours of the onset of chest pain. Complications, such as recurrent chest pain, associated with extension of myocardial necrosis can be identified and assessed. The total praecordial changes in R/S ratio and Q wave amplitude correlate with the total MB fraction of creatine kinase activity released into the plasma in 20 patients after uncomplicated anterior infarction. This technique for identifying those factors that may modify the progressive loss of active myocardium in the early phase of acute infarction of the heart is noninvasive and repeatable.

In patients with acute myocardial infarction the extent of tissue damage is important in relation to morbidity and mortality. Recently research has been directed to the development of techniques and interventions that will lead to the salvage of active myocardium in acute infarction (Maroko *et al.*, 1971; Maroko, 1974).

The electrocardiogram undergoes a series of changes after the onset of acute regional myocardial ischaemia (Johnston *et al.*, 1935; Wilson *et al.*, 1935a, b). The localised loss of R waves and the appearance of Q waves is thought to represent the loss of electrically active myocardium (Johnston *et al.*, 1935; Wilson *et al.*, 1935a; Prinzmetal *et al.*, 1954; Shaw *et al.*, 1954; Selwyn and Shillingford, 1977). Praecordial surface mapping of the electrocardiogram in man has been developed to follow the changes in R/S ratio, and amplitude of R and Q waves during acute myocardial infarction (Selwyn and Shillingford, 1977).

It is the purpose of this paper to describe the pattern and time course of the loss of electrically active myocardium in a group of patients with uncomplicated anterior infarction. A relation is shown between these changes in the praecordial map and the extent of cell necrosis assessed by the total release of the myocardial fraction of creatine kinase (MB CK). The significance of the loss of R waves and the appearance of Q waves in relation to the underlying pathology and the possibility of limiting infarct size by therapeutic intervention is discussed.

Patients and methods

The 45 patients (34 men and 11 women, aged between 42 and 74 years, mean 55 years) were admitted to the coronary care unit at the Hammersmith Hospital with a clinical diagnosis of acute anterior myocardial infarction. All these patients developed electrocardiographic evidence of acute myocardial infarction on the standard 12-lead electrocardiogram and all had a diagnostic rise in serum enzymes. While in the coronary care unit, 40 of the patients did not develop any of the following major complications: (a) recurrent chest pain lasting more than 10 minutes after the initial episode of pain; (b) clinical or chest *x*-ray evidence of congestive heart failure or pulmonary oedema; or (c) cardiac rhythm disturbances other than isolated unifocal ventricular ectopic beats. Five of the 45 patients had a number of complications after admission to the coronary care unit. These were: (a) recurrent chest pain 4 to 12 hours after the onset of the first episode in 3 patients; and (b) ventricular fibrillation followed by recovery in 2.

Praecordial electrocardiographic maps were recorded on admission, again at 1 hour, then 4-hourly for 12 hours, and daily thereafter. Additional readings were made if the clinical condition changed. Recordings were made using a direct writing ink jet electrocardiograph (Elema-Schonander Mingograph) on 3 channels simultaneously. The gain employed was 10 mm for 1 mV and the paper speed was 25 mm per second. Welsh suction type electrodes with a contact diameter of 1 cm were used. Electrocardiograms were recorded from

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72 points distributed evenly over the praecordium as described by Reid *et al.* (1971).

The amplitude of the R and S waves was measured in millimetres to the nearest 0·5 mm using the TP segment as the isoelectric line, or the PQ segment when there was no isoelectric TP segment as a result of tachycardia. The R/S ratio was calculated at each of the 72 positions. The R wave amplitude in millimetres was used in place of R/S ratio from those sites where the S wave measured less than 0·5 mm. Maps were always recorded with the patients at rest at 45°. The R/S ratios were recorded on a standard diagram in which the 72 points were shown at 1 cm intervals (Selwyn and Shillingford, 1977). The appearance of QRS widening, bundle-branch block, or pathological axis changes can alter the R/S ratio and R wave amplitude. Patients whose electrocardiograms showed QRS widening beyond 110 ms or pathological axis changes beyond 30° to 130° in the frontal plane were therefore excluded from this study. Pathological Q waves were identified using Minnesota code criteria (Blackburn *et al.*, 1960; Rose and Blackburn, 1968).

Praecordial maps were recorded from 10 men and 10 women who had no evidence of cardiovascular disease on history, physical examination, chest *x*-ray film, or electrocardiogram. The age of the subjects in this control group was evenly distributed between 20 and 70 years. The mean, 68 per cent, and 95 per cent confidence limits (log normal distribution) of the 20 R/S ratios at each of the 72 positions of the praecordial electrocardiogram were calculated. The 72 mean R/S ratios obtained from the normal group were used to calculate a single mean and standard error for the R/S ratio of the whole praecordial map. The reproducibility of praecordial mapping has already been reported (Selwyn and Shillingford, 1977; Selwyn *et al.*, 1977). The surface maps produced in this way from patients suffering acute infarction show areas of Q waves, QR or Qr waves, R/S ratios with loss of R wave up to and beyond the 95 per cent confidence limit of the normal group, R/S ratios with loss of R wave up to and beyond the 68 per cent confidence limit of the normal group.

The serial measurements of mean praecordial R/S ratio (as shown in Fig. 3 and 4A were used to display the time course for the regional praecordial loss of R waves in the patients suffering acute infarction. This does not include the development of Q waves.

Five ml of venous blood samples (taken at 3 hours intervals for the first 24 hours after the onset of chest pain, then 6 hourly for 4 days) were drawn from 20 of the 40 patients with uncomplicated infarction and from the 5 patients with complications. These samples were placed in lithium heparin tubes and centrifuged at 2000 *g* for 10 minutes. Total plasma CK activity was measured spectrophotometrically (Cecil 272 system spectrophotometer, Cecil Instruments, Cambridge) by the method of Oliver (1955) as modified by Hearse *et al.* (1973). Using this method the upper limit of plasma CK for healthy subjects is 50 mU/ml (Ogunro *et al.*, 1977).

Samples with activity 250 mU/ml or more were diluted before determination of total CK. In order to minimise the dilution-activation effect observed with plasma CK, heat inactivated plasma was used as diluent (Craig *et al.*, 1967). Isoenzymes were separated by electrophoresis on agarose gels and quantified in aqueous solution by fluorimetry (Ogunro *et al.*, 1977). This measurement is sensitive, specific, and linear (Ogunro *et al.*, 1977). MB CK isoenzyme release curves were constructed by measuring the plasma MB CK activity (mU/ml) at stated time intervals after the onset of chest pain. The area under each curve was used as an index of the total activity of MB CK released into the plasma.

In order to test the significance of changes in R/S ratio, and of amplitude of R and Q waves, an analysis of variance was used. The variables included in this test were time, posture, respiration, and replacing electrodes. A two-tail test of significance was used to assess the difference between the complicated and uncomplicated groups.

Results

Previous studies of the reproducibility of praecordial mapping have shown that variables such as change in posture and phase of respiration have a significant effect and must be taken into account when assessing electrocardiographic changes caused by cardiac events (Selwyn and Shillingford, 1977; Selwyn *et al.*, 1977). The distribution of praecordial R/S ratios for the 20 normal individuals with no cardiovascular disease was log normal, and is shown for the 9 positions of row D of the praecordial map in Fig. 1A. Similar figures were constructed for the remaining horizontal rows of the surface map (Selwyn and Shillingford, 1977). The mean value of the R/S ratio at each of the 72 positions of the praecordial map in the control group was used to calculate a single mean R/S ratio ± SEM for the whole praecordial map. In the normal group this was 4·2 ±0·46.

UNCOMPLICATED GROUP

Fig. 1B shows the serial changes in R/S ratio, and

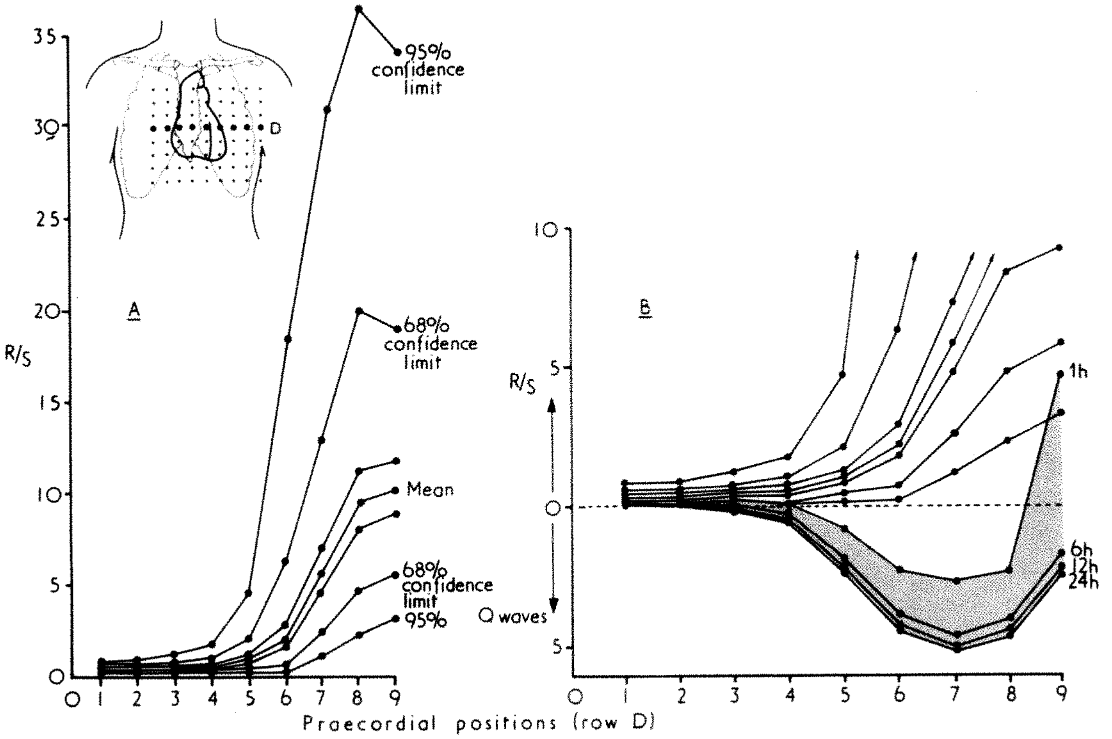

Fig. 1 *(A) The praecordial R/S ratios from the 9 positions of horizontal row D in 20 individuals with no evidence of cardiovascular disease. (B) The praecordial R/S ratios from the 9 positions of row D showing the normal range and the changing pattern in 4 praecordial maps taken from a patient with anterior infarction. Positive values show R/S ratios and negative values show the pathological Q waves.*

Q wave amplitude at the 9 positions of row D in 4 praecordial maps from a patient with uncomplicated anterior infarction. Fig. 2 shows the serial changes in the praecordial maps in a patient with uncomplicated anterior myocardial infarction. Fig. 3 shows the mean R/S ratio ± SEM for all the praecordial maps in the control group: these show a ±4 per cent variation when these individuals are mapped over 4 days (Selwyn and Shillingford, 1977). Fig. 3 also shows the mean R/S ratio ± SEM calculated from the group of patients with uncomplicated anterior myocardial infarction. The number of patients available for study in each time interval after the onset of chest pain is indicated. The R/S ratio in 3 of the 6 patients mapped in the first hour from the onset of chest pain showed an increase from 3·7 ± 0·1 to 4·4 ± 0·2. These 3 patients were studied within 20 minutes from the onset of chest pain. The R/S ratio then showed a rapid decrease from 3·5 ± 0·3 to 1·85 ± 0·7 mm between the first and sixth hour after the onset of chest pain. After 12 hours changes in R/S ratio were small, difficult to detect, and approached the ±4 per cent variation of the technique. Q waves appeared in the praecordial maps at 112 ± 5·3 minutes.

Fig. 4A shows these serial changes in R/S ratio in the uncomplicated group and also the serial changes in a patient with anterior infarction who had a second episode of chest pain 12 hours after the onset of the initial pain. The changes seen in mean praecordial R/S ratio in the uncomplicated group were significantly different from those in the 5 individuals who had complications (MD = 1·10, T = 18·9, P = < 0·001). Fig. 4B shows the pattern and time course of plasma MB CK activity in 20 of the 40 patients with uncomplicated anterior infarction. This is also shown for the same patient with recurrent chest pain, and differed significantly from that of the uncomplicated group, suggesting a second episode of necrosis.

Fig. 5 shows the serial praecordial surface maps in this patient and shows the extension of the area of Q waves, Qr waves, and R/S ratio loss.

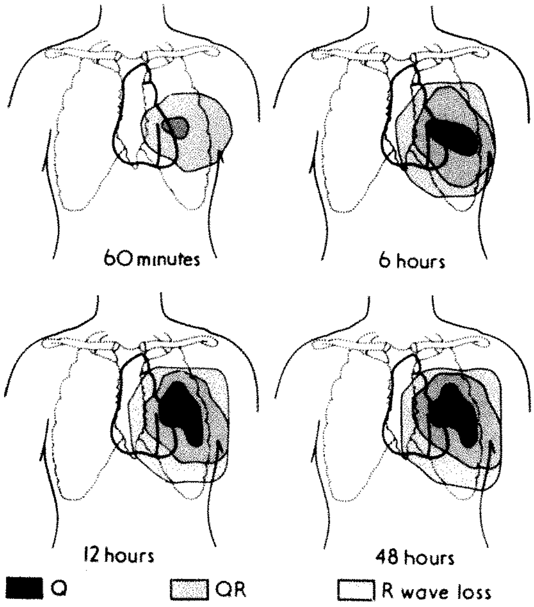

Fig. 2 *Serial praecordial surface maps from a patient with uncomplicated anterior infarction. The rapid loss of R waves and appearance of Q waves occur within 6 hours from the onset of chest pain. R wave loss implies decrease in R/S outside 95 per cent confidence limits (or r < 0·5).*

Fig. 6 shows a relation between the total MB CK activity released and the mean R/S ratio at 24 hours in patients with anterior infarction ($P = < 0{\cdot}001$, $R = -0{\cdot}89$, $N = 20$).

Discussion

Wilson *et al.* (1935a) showed that loss of R wave amplitude occurred in the epicardial leads over

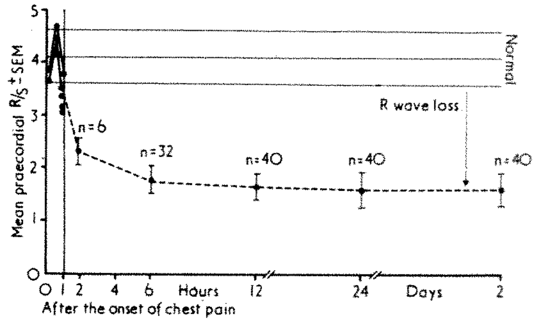

Fig. 3 *Mean ± SEM praecordial R/S ratio in 40 patients with uncomplicated anterior infarction is shown at specified times after the onset of chest pain. The number of patients (n) available for study at each time is shown above. Mean ± SEM of the praecordial R/S ratio in the normal group is also shown.*

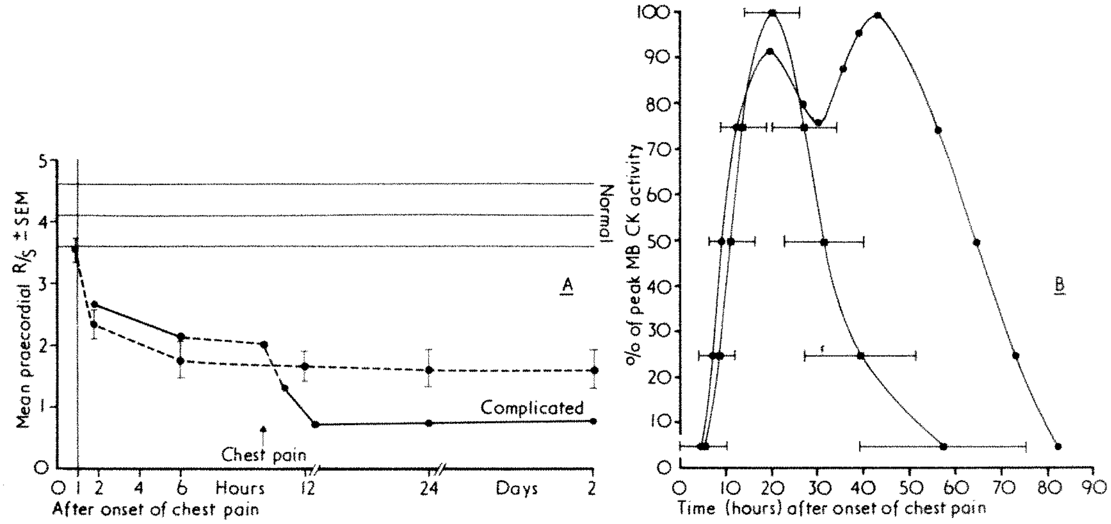

Fig. 4 *(A) The changes seen in the mean ± SEM of the praecordial R/S ratios in 40 patients with uncomplicated anterior infarction are shown. The changes in the mean R/S ratio in a patient with recurrent chest pain 12 hours after the initial episode shows further reduction in R/S ratio. (B) Serial plasma MB CK activity (expressed as a percentage of the peak value) in patients with uncomplicated infarction and in the patient illustrated in (A) with recurrent chest pain. The time taken for the plasma MB CK activity to reach 5, 25, 50, 75, and 100 per cent of the peak value is plotted for the release and clearance phases of the curves; the mean ± 2 SD is shown for the uncomplicated group.*

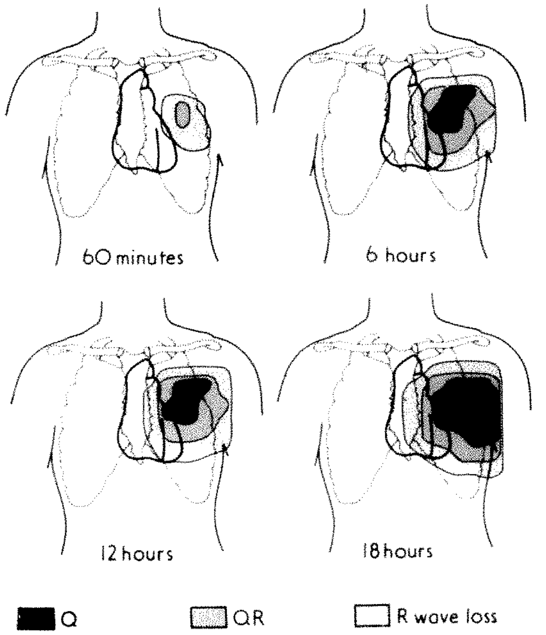

Fig. 5 *Serial praecordial surface maps in the same patient with anterior infarction who had recurrent chest pain at 12 hours. These show a significant extension of the areas in which loss of R waves and development of Q waves are seen. This did not occur in the uncomplicated group (Fig. 2) and is associated with the abnormal MB CK release curve (Fig. 4B).*

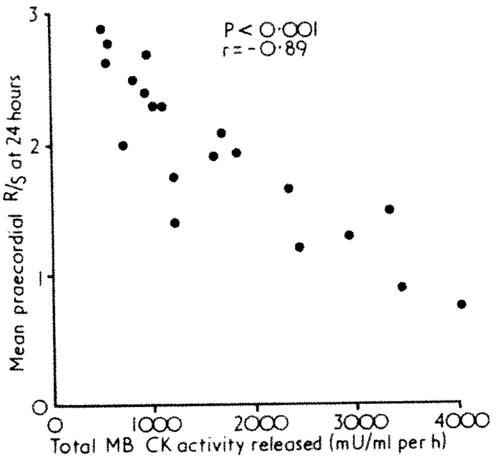

Fig. 6 *The relation between the reduction in R/S ratio on the praecordial map seen at 24 hours and the total release of MB CK activity in the plasma in patients with anterior infarction was significant.*

ischaemic myocardium and concluded that this was the result of the absence of electrical forces normally produced by the portion of ventricular wall deprived of its blood supply. Studies have shown that a reduction of R wave voltage is found at sites in which ischaemia produced a mixture of viable and necrotic myocardium (Prinzmetal *et al.*, 1954; Shaw *et al.*, 1954). In this study a range of values of R/S ratio and R waves for the 72 point praecordial map has been determined for a group of people with no detectable cardiovascular disease. These findings in normal subjects at rest and in the same position did not vary more than ±4 per cent when maps were repeated over many days, and Qr and Q waves were not seen in this normal group. In contrast to this, the group with anterior infarction showed serially, changing abnormal areas of R/S ratio, and Qr and Q waves which can be outlined on surface maps.

In a group of patients with uncomplicated anterior infarction, serial mapping of the praecordial electrocardiogram showed an initial increase in R wave amplitude in 3 patients mapped within 20 minutes from the onset of chest pain (Fig. 3). Significant loss of R wave was detectable at 30 minutes and was complete within 6 hours of the onset of chest pain. After 12 hours from the onset of chest pain changes in R/S ratio, and fresh appearance of Q waves could not be detected with this technique.

ST segment elevation in acute regional myocardial ischaemia has been widely studied (Samson and Scher, 1960; Maroko *et al.*, 1971; Muller *et al.*, 1975); however, in experimental work it does not provide direct information about the death of myocardium, and in clinical practice it cannot be used to assess the progressive loss of active myocardium in acute infarction (Reese *et al.*, 1973; Norris *et al.*, 1976; Selwyn *et al.*, 1977).

The location and distribution of the praecordial electrocardiographic changes depend on the site of the ischaemic area and the position of the heart in relation to the 72 points on the chest, and on the distance between the electrodes and the heart and the resistance of the tissues between. The borders of the electrocardiographic manifestations of ischaemia will be influenced by the intervening normal tissue. Accepting these reservations, experimental research has shown a close correlation between the epicardial and praecordial electrocardiographic R wave and ST segment changes during ischaemia (Muller *et al.*, 1975).

In conclusion, this study has shown that praecordial mapping of the electrocardiogram provides a repeatable and noninvasive assessment of the progressive loss of electrically active myocardium in patients with anterior infarction. MB CK is essentially cardiospecific and the total amount of various enzymes released into the plasma provides a quantitative assessment of the extent of muscle necrosis in acute myocardial infarction (Sobel *et al.*, 1972; Mathey *et al.*, 1974). We have shown that the loss of R wave voltage and development of Q waves were complete by 24 hours and that the extent of these changes correlated with the total MB CK activity released into the plasma.

Serial observations on the loss of R waves and appearance of Q waves in 40 patients with uncomplicated anterior infarction suggest that in this group the loss of electrically active myocardium occurs within 6 hours from the onset of chest pain. The technique makes it possible to assess complications that may be associated with extension of the loss of active myocardium, and may prove useful in identifying those factors that modify the progress of cell death and loss of viable tissue in the early phase of acute infarction and thus in limiting infarct size.

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References

Blackburn, H., Keys, A., Simonson, E., Rautaharju, P., and Punsar, S. (1960). The electrocardiogram in population studies. *Circulation*, **21**, 1160–1175.

Craig, F. A., Smith, J. C., and Foldes, F. F. (1967). Effect of dilution on the activity of serum creatine phosphokinase. *Clinica Chimica Acta*, **15**, 107–111.

Hearse, D. J., Humphrey, S. M., and Chain, E. B. (1973). Abrupt reoxygenation of the anoxic potassium-arrested perfused rat heart: a study of myocardial enzyme release. *Journal of Molecular and Cellular Cardiology*, **5**, 395–407.

Johnston, F. D., Hill, I. G. W., and Wilson, F. N. (1935). The form of the electrocardiogram in experimental myocardial infarction. II. The early effects produced by ligation of the anterior descending branch of the left coronary artery. *American Heart Journal*, **10**, 889–902.

Maroko, P. R. (1974). Assessing myocardial damage in acute infarcts. Editorial. *New England Journal of Medicine*, **290**, 158–159.

Maroko, P. R., Kjekshus, J. K., Sobel, B. E., Watanabe, T., Covell, J. W., Ross, J., and Braunwald, E. (1971). Factors influencing infarct size following experimental coronary artery occlusions. *Circulation*, **43**, 67–82.

Mathey, D., Bleifeld, W., Hanrath, W., and Effert, S. (1974). Attempt to quantitate relation between cardiac function and infarct size in acute myocardial infarction. *British Heart Journal*, **36**, 271–279.

Muller, J. E., Maroko, P. R., and Braunwald, E. (1975). Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischemic injury. *Circulation*, **52**, 16–27.

Norris, R. M., Barratt-Boyes, C., Heng, M. K., and Singh, B. N. (1976). Failure of ST segment elevation to predict severity of acute myocardial infarction. *British Heart Journal*, **38**, 85–92.

Ogunro, E. A., Hearse, D. J., and Shillingford, J. P. (1977). Creatine kinase isoenzymes: their separation and quantitation. *Cardiovascular Research*, **11**, 94–102.

Oliver, I. T. (1955). A spectrophotometric method for the determination of creatine phosphokinase and myokinase. *Biochemical Journal*, **61**, 116–122.

Prinzmetal, M., Shaw, C. McK., Maxwell, M. H., Flamm, E. J., Goldman, A., Kimura, N., Rakita, L., Borduas, J-L., Rothman, S., and Kennamer, R. (1954). Studies on the mechanisms of ventricular activity IV. *American Journal of Medicine*, **16**, 469–489.

Reese, L., Scheidt, S., and Killip, T. (1973). Variability of precordial ST segment maps after acute myocardial infarction in man (abstract). *Circulation*, **47–48**, Suppl. IV, 38.

Reid, D. S., Pelides, L. J., and Shillingford, J. P. (1971). Surface mapping of the RS-T segment in acute myocardial infarction. *British Heart Journal*, **33**, 370–374.

Rose, G. A., and Blackburn, H. (1968). Cardiovascular survey methods. *World Health Organization. Monograph Series*, No. 56. Geneva.

Samson, W. E., and Scher, A. M. (1960). Mechanism of S-T segment alteration during acute myocardial injury. *Circulation Research*, **8**, 780–787.

Selwyn, A. P., Ogunro, E., and Shillingford, J. P. (1977). Natural history and evaluation of ST segment changes and MB CK release in acute myocardial infarction. *British Heart Journal*, **39**, 988–994.

Selwyn, A. P., and Shillingford, J. P. (1977). Praecordial mapping of Q waves and RS ratio changes in acute myocardial infarction. *Cardiovascular Research*, **11**, 167–171.

Shaw, C. McK., Goldman, A., Kennamer, R., Kimura, N., Lindgren, I., Maxwell, M. H., and Prinzmetal, M. (1954). Studies on the mechanism of ventricular activity. VIII. The origin of the coronary QR wave. *American Journal of Medicine*, **16**, 490–503.

Sobel, B. E., Bresnahan, G. F., Shell, W. E., and Yoder, R. D. (1972). Estimation of infarct size in man and its relation to prognosis. *Circulation*, **46**, 640–648.

Wilson, F. N., Hill, I. G. W., and Johnson, F. D. (1935a). The form of the electrocardiogram in experimental myocardial infarction. III. The later effects produced by ligation of the anterior descending branch of the left coronary artery. *American Heart Journal*, **10**, 903–915.

Wilson, F. N., Johnston, F. D., and Hill, I. G. W. (1935b). The form of the electrocardiogram in experimental myocardial infarction. IV. Additional observations on the later effects produced by ligation of the anterior descending branch of the left coronary artery. *American Heart Journal*, **10**, 1025–1041.

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Prognostic significance of isolated left anterior hemiblock and left axis deviation in the course of acute myocardial infarction[1]

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In 700 patients with acute myocardial infarction admitted to the intensive coronary care unit of our hospital, the incidence and significance of left anterior hemiblock and left axis deviation has been studied in the acute phase of disease. In 102 (14·6%) of the 700 patients, isolated left axis deviation (mean QRS axis −45°) was found and 69 of them (9·9%) met the criteria of left anterior hemiblock. Of the 69 patients with left anterior hemiblock, 61 had acute anterior myocardial infarction, 5 had inferior infarction, and 3 had subendocardial infarction. The left anterior hemiblock was transient in 5 patients, but persisted in 64. All patients with and without isolated left anterior hemiblock and left axis deviation were compared statistically with reference to mortality rate and the incidence of arrythmias; no significant difference was noted. However, in patients over the age of 65 and also in those with hypertension, the incidence of left axis deviation was significantly higher ($P<0{\cdot}05$ and $P<0{\cdot}001$, respectively).

It was concluded that isolated left anterior hemiblock and left axis deviation occurring in the course of acute myocardial infarction had no influence on the prognosis of acute myocardial infarction.

Intensive studies have been made on the intraventricular blocks occurring in the course of acute myocardial infarction. These studies showed that complete bundle-branch blocks (Bauer *et al.*, 1965; Hunt and Sloman, 1969; Godman *et al.*, 1970; Norris and Croxson, 1970) and incomplete bifascicular block have adverse effects on the prognosis of acute myocardial infarction (Kulbertus and Collignon, 1969; Watt and Pruitt, 1969; Atkins *et al.*, 1970; Castellanos *et al.*, 1970; Roos and Dunning, 1970; Scanlon *et al.*, 1970). Investigations concerning prognostic significance of isolated left anterior hemiblock and left axis deviation are rare. Reports published on this type of conduction defect revealed that it had no adverse effect on the prognosis of acute myocardial infarction (Pryor and Blount, 1966; Marriott and Hogan, 1970; Col and Weinberg, 1972; Kincaid and Botti, 1972).

The aim of the work presented here was to study the effects of isolated left anterior hemiblock and left axis deviation on the course and prognosis of acute myocardial infarction.

Subjects and methods

The hospital records of 700 patients admitted to the intensive coronary care unit with evidence of acute myocardial infarction during a 5-year period from January 1969 to January 1975 were studied in detail. Of these 700 patients, 116 were women aged 42 to 88 years (average 62·4 years), and 584 were men aged 29 to 86 years (average 55·7 years). The age of the whole series ranged from 29 to 88 years (average 57·9). The diagnosis of acute myocardial infarction was based on the history, physical signs, and electrocardiographic and serum enzyme changes, and other related laboratory investigations (World Health Organization, 1971). The 12-lead serial electrocardiograms and single lead monitor records were used for the analysis of the rhythm and conduction disturbances.

All patients with a mean frontal plane QRS axis of −45° or more leftward and normal QRS duration were included in this study. This group of patients with left axis deviation was further subdivided into 69 patients with and 33 patients without electrocardiographic signs of classic left anterior hemiblock. The terminology and criteria for conduction

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defect in the left anterior fascicle were taken from Rosenbaum *et al.* (1970), Pryor (1971), and Rosenbaum *et al.* (1972). Those patients with a mean frontal plane QRS axis of –45° or more leftward, and initial right inferior vector with r waves in leads II, III, aVF, and with a Q wave in lead aVL, followed by a left superior vector, were included in this subgroup of patients with left anterior hemiblock. Those patients with left axis deviation with QS complexes and with no terminal R waves in leads II, III, and aVF were accepted as having a combination of an old inferior myocardial infarction and left anterior hemiblock (Rosenbaum *et al.*, 1969a, 1970; Marriott and Hogan, 1970; Castellanos *et al.*, 1971; Benchimol *et al.*, 1972; Rosenbaum *et al.*, 1972; Schamroth, 1975). Those with left axis deviation but not meeting the criteria for left anterior hemiblock were included in the second subgroup. The patients in the latter group (without signs of left anterior hemiblock) had no Q waves in aVL or had small Q waves in leads II, III, and aVF.

Results

Of the 700 patients with acute myocardial infarction, 102 (14·6%) had frontal plane left axis deviation (–45° or more leftward). Of these 102 patients, 69 (9·9%) had classic left anterior hemiblock, 25 (3·6%) had left axis deviation with Q waves in II, III, and aVF, and the remaining 8 (1·1%) had left axis deviation with no Q waves in leads I and aVL.

Table 1 *Hospital mortality of patients*

	Patients (No)	*Deaths (No)*	*Mortality %*
Total	700	98	14·0
With LAD but without bundle-branch block	102	12	11·8
Remainder	598	86	14·4
With no intraventricular conduction defect	504	61	12·1
With LAHB	69	9	13·0
With LAD but no Q wave in aVL	8	1	12·5
With LAD but Q waves in II, aVF	25	2	8·0

LAD, left axis deviation; LAHB, left anterior hemiblock.

MORTALITY

During this 5-year period the overall mortality rate for our 700 patients with acute myocardial infarction was 14 per cent (98 deaths) (Table 1). However, the mortality rate for 102 patients with left axis deviation was 11·8 per cent (12 deaths) and for 69 patients with isolated left anterior hemiblock was 13 per cent (9 deaths). Thus, on our series the mortality rate was not increased in the presence of left axis deviation and/or left anterior hemiblock ($P < 0·9$).

ASSOCIATED ARRHYTHMIAS

Table 2 compares the different groups with regard to development of arrhythmias during the course of acute myocardial infarction while the patients were in the intensive coronary care unit. The patients with isolated left anterior hemiblock or left axis deviation without left anterior hemiblock did not have an increased incidence of atrioventricular block, atrial fibrillation, atrial flutter, or ventricular premature beats. Ventricular tachycardia seemed to occur more frequently in the group with left anterior hemiblock though the difference was not significant. The 61 patients with an acute anterior myocardial infarction with left anterior hemiblock was compared with 262 patients with acute anterior myocardial infarction without left anterior hemiblock to assess the development of arrhythmias. Again, no significant difference was observed between these comparable groups (Table 3).

SITE OF INFARCTION

Of the 69 patients with isolated left anterior hemiblock, 61 (88%) had an anteroseptal myocardial infarction, 5 (7·2%) had inferior myocardial infarction, 3 (4·3%) had subendocardial (nontransmural) infarction, and 7 (10·1%) had a history of multiple infarctions. Of the 33 patients with left axis deviation without left anterior hemiblock, 21 (63·6%) had inferior myocardial infarction, 6 (18·2%) had anteroseptal infarction, 6 (18·2%) had subendocardial infarction, and 12 (36·4%) had multiple infarctions.

Table 2 *Incidence of arrhythmias*

	Overall series %	*Without LAD %*	*LAD series %*	*LAHB series %*	*LAD without LAHB %*
AV block	23·6	23·6	23·4	21·1	30·3
Atrial fibrillation	12·2	12·7	9·8	10·1	9·0
Ventricular premature beats	41·8	42·3	39·2	44·9	27·2
Ventricular tachycardia	14·1	13·1	22·5	24·6	18·1
Ventricular fibrillation	7·5	7·1	9·8	10·1	9·0

DURATION OF HEMIBLOCK

Transient left anterior hemiblock appeared in 5 cases during the course of myocardial infarction and persisted from 10 hours to 11 days.

ASSOCIATED CLINICAL FEATURES

Other characteristics of the 'coronary prone' patient were compared for the groups of patients with and without left axis deviation and left anterior hemiblock (Table 4). There were no significant differences with regard to age, diabetes mellitus, history of previous myocardial infarction, hypertension, cigarette smoking, obesity. It was noted, however, that left axis deviation occurred significantly more often in hypertensive patients over the age of 65 ($P < 0{\cdot}001$).

Discussion

Left anterior hemiblock is the most frequent type of intraventricular block found in the course of acute myocardial infarction. Working on this same subject, the incidence reported by Marriott and Hogan (1970) in a series of 250 cases was 15·2 per cent, by Scheinman and Brenman (1972) in a series of 480 cases the incidence was 4 per cent, and by Col and Weinberg (1972) in a series of 225 cases it was 6·2 per cent. In our series of 700 patients isolated left anterior hemiblock developed in 9·9 per cent. The frequent appearance of left anterior hemiblock in acute myocardial infarction is explained by a discrete left anterior fascicle. The thin structure of this fascicle receiving its blood supply mainly from the anterior descending artery is often vulnerable to ischaemic and necrotic insults (Lenegre, 1964; Sutton and Davies, 1968; Massing and James, 1971). If the left anterior fascicle is not a discrete structure an infarction large enough to deviate the axis abnormally leftward could result in a dangerous situation.

Table 3 *Comparison of incidence of arrhythmias in patients with LAHB and without intraventricular conduction defect*

	Anterior MI with LAHB %	*Anterior MI without IV conduction defect* %
AV block	19·7	12·6
Atrial fibrillation	11·4	12·2
Ventricular premature beats	47·5	50·7
Ventricular tachycardia	24·5	19·0
Ventricular fibrillation	8·1	10·3
Total number	61	262

Table 4 *Comparison of characteristics of patients with and without LAD and LAHB*

	Total series	*Without LAD*	*LAD series*	*LAHB series*
Number of patients	700	598	102	69
Average age	57·9	57·4	58·5	58·6
Diabetes mellitus %	21·0	20·7	22·5	24·6
Previous MI %	23·4	24·2	18·6	10·1
Hypertension %	36·2	34·2	48·0	43·4
Smoking %	78·7	78·4	80·3	72·4
Obesity %	21·0	20·4	24·5	23·1

It was shown that the occurrence of isolated left axis deviation with or without the criteria for left anterior hemiblock did not increase the rate of mortality. Marriott and Hogan (1970) and Kincaid and Botti (1972) reported earlier also that left axis deviation in the course of acute myocardial infarction had no adverse effect on the prognosis. The reason why left anterior hemiblock is not a serious conduction disturbance is not known, for it would be expected that any type of conduction disturbance occurring in the course of acute myocardial infarction would increase the risk of the disease. Furthermore, it is known definitely that the appearance of complete right bundle-branch block or left bundle-branch block increases the rate of mortality in acute myocardial infarction (Bauer *et al.*, 1965; Hunt and Sloman, 1969; Godman *et al.*, 1970; Norris and Croxson, 1970). In brief, it is suggested that left anterior hemiblock has no adverse effect on mortality because (1) left anterior fascicle has a separate and thin structure differing from the rest of the left bundle, making it vulnerable to only slight ischaemia or necrosis (Massing and James, 1971) and (2) only a small conduction delay which does not lead to prolonged QRS duration should pose no problem (Kincaid and Botti, 1972).

In our patients the development of left anterior hemiblock did not increase the incidence of arrhythmias and particularly the incidence of atrioventricular block. This finding confirms similar earlier reports (Marriott and Hogan, 1970; Col and Weinberg, 1972; Kincaid and Botti, 1972). We compared the development of arrhythmias in 61 patients with acute anterior myocardial infarction with left anterior hemiblock with 262 patients with acute anterior myocardial infarction without intraventricular block. Atrioventricular block in the former group was found in 12 patients (19·7%) and in the latter in 33 (12·6%). The difference between the two groups was not statistically significant. There was also no difference in other types of arrhythmias. Nor did the left axis deviation increase the incidence of arrhythmias.

When other clinical features were compared between the groups with and without left anterior hemiblock and left axis deviation no significant difference was noted, the only difference was the frequency of hypertension in patients with left axis deviation over 65 years ($P < 0.001$). In a similar study (Kincaid and Botti, 1972) cardiomegaly was found to be more frequent in the group with left axis deviation.

In our series 5 instances of transient left anterior hemiblock developed during the course of acute myocardial infarction. Transient left anterior hemiblock was also reported by others in the course of acute myocardial infarction (Rosenbaum *et al.*, 1969b) and as a result of metabolic factors (Deliyannis *et al.*, 1971; Ewy *et al.*, 1971). As reported previously, transient left anterior hemiblock has no adverse effect on the prognosis of the disease.

It is concluded that isolated left anterior hemiblock and left axis deviation complicating acute myocardial infarction are common, occur early during its evolution, may rarely be transient, and do not seem to affect the clinical course or increase the mortality of the disease.

References

Atkins, J. M., Leshin, S. J., Blomqvist, G., and Mullins, C. B. (1970). Prognosis of right bundle branch block and left anterior hemiblock: a new indication for permanent pacing (abstract). *American Journal of Cardiology*, **26**, 624.

Bauer, G. E., Julian, D. G., and Valentine, P. A. (1965). Bundle-branch block in acute myocardial infarction. *British Heart Journal*, **27**, 724–730.

Benchimol, A., Desser, K. B., and Massey, B. J. (1972). Coexisting left anterior hemiblock and inferior wall myocardial infarction. Vectorcardiographic features. *American Journal of Cardiology*, **29**, 7–14.

Castellanos, A., Jr., Chahine, R. A., Chapunoff, E., Gomez, J., and Portillo, B. (1971). Diagnosis of left anterior hemiblock in the presence of inferior wall myocardial infarction. *Chest*, **60**, 543–551.

Castellanos, A., Jr., Maytin, O., Arcebal, A. G., and Lemberg, L. (1970). Significance of complete right bundle branch block with right axis deviation in the absence of right ventricular hypertrophy. *British Heart Journal*, **32**, 85–92.

Col, J. J., and Weinberg, S. L. (1972). The incidence and mortality of intraventricular conduction defects in acute myocardial infarction. *American Journal of Cardiology*, **29**, 344–350.

Deliyannis, A. A., Symvoulidis, A. D., and Symvoulidis, D. M. (1971). Electrocardiographic QRS axis shift with left anterior hemiblock (letter). *Journal of the American Medical Association*, **217**, 341.

Ewy, G. A., Karliner, J., and Bedynek, J. L. (1971). Electrocardiographic QRS axis shift as a manifestation of hyperkalemia. *Journal of the American Medical Association*, **215**, 429–432.

Godman, M. J., Lassers, B. W., and Julian, D. G. (1970). Complete bundle-branch block complicating acute myocardial infarction. *New England Journal of Medicine*, **282**, 237–240.

Hunt, D., and Sloman, G. (1969). Bundle-branch block in acute myocardial infarction. *British Medical Journal*, **1**, 85–88.

Kincaid, D. T., and Botti, R. E. (1972). Significance of isolated left anterior hemiblock and left axis deviation during acute myocardial infarction. *American Journal of Cardiology*, **30**, 797-800.

Kulbertus, H., and Collignon, P. (1969). Association of right bundle-branch block with left superior or inferior intraventricular block: its relation to complete heart block and Adams-Stokes syndrome. *British Heart Journal*, **31**, 435–440.

Lenegre, J. (1964). Etiology and pathology of bilateral bundle-branch block in relation to complete heart block. *Progress in Cardiovascular Diseases*, **6**, 409–444.

Marriott, H. J. L., and Hogan, P. (1970). Hemiblock in acute myocardial infarction. *Chest*, **58**, 342–344.

Massing, G. K., and James, T. N. (1971). Anatomical configuration of the His bundle and proximal bundle branches in the human heart. *Circulation*, **43-44**, Suppl. 2, 64.

Norris, R. M., and Croxson, M. S. (1970). Bundle-branch block in acute myocardial infarction. *American Heart Journal*, **79**, 728–733.

Pryor, R. (1971). Fascicular blocks: criteria for diagnosis. *Medical World News, Cardiovascular Review*, pp. 26–31.

Pryor, R., and Blount, S. G., Jr. (1966). The clinical significance of true left axis deviation. Left intraventricular blocks. *American Heart Journal*, **72**, 391–413.

Roos, J. C., and Dunning, A. J. (1970). Right bundle-branch block and left axis deviation in acute myocardial infarction. *British Heart Journal*, **32**, 847–851.

Rosenbaum, M. B., Elizari, M. V., and Lázzari, J. O. (1970). *The Hemiblocks*, pp. 1–17. Tampa Tracings, Oldsmar, Florida.

Rosenbaum, M. B., Elizari, M. V., Lázzari, J. O., Nau, G. J., Halpern, M. S., and Levi, R. J. (1972). The differential electrocardiographic manifestations of hemiblocks, bilateral bundle branch block and trifascicular blocks. In *Advances in Electrocardiography*, p. 145. Ed. by R. C. Schlant and J. W. Hurst. Grune and Stratton, New York.

Rosenbaum, M. B., Elizari, M. V., Lázzari, J. O., Nau, G. J., Levi, R. J., and Halpern, M. S. (1969a). Intraventricular trifascicular blocks. Review of the literature and classification. *American Heart Journal*, **78**, 450–459.

Rosenbaum, M. B., Elizari, M. V., Levi, R. J., Nau, G. J., Pisani, N., Lázzari, J. O., and Halpern, M. S. (1969b). Five cases of intermittent left anterior hemiblock. *American Journal of Cardiology*, **24**, 1–7.

Scanlon, P. J., Pryor, R., and Blount, S. G., Jr. (1970). Right bundle-branch block associated with left superior or inferior intraventricular block. *Circulation*, **42**, 1135–1142.

Schamroth, L. (1975). *The Electrocardiology of Coronary Artery Disease*, pp. 109–121. Blackwell Scientific Publications, Oxford.

Scheinman, M., and Brenman, B. (1972). Clinical and anatomic implications of intraventricular conduction block in acute myocardial infarction. *Circulation*, **46**, 753–760.

Sutton, R., and Davies, M. (1968). The conduction system in acute myocardial infarction complicated by heart block. *Circulation*, **38**, 987–992.

Watt, T. B., and Pruitt, R. D. (1969). Character, cause and consequence of combined left axis deviation and right bundle-branch block in human electrocardiograms. *American Heart Journal*, **77**, 460–465.

World Health Organization, Regional Office for Europe (1971). *Ischaemic Heart Disease Registers: Report of the Fifth Working Group, Copenhagen, 26-29 April 1971, Copenhagen.*

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Comparison of haemodynamic effects of phentolamine, sodium nitroprusside, and glyceryl trinitrate in acute myocardial infarction

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The effects of the commonly employed systemic vasodilators phentolamine, nitroprusside, and intravenous glyceryl trinitrate on cardiac performance, peripheral resistance, and vascular capacitance, as judged by changes in left ventricular filling pressure, were compared in 29 patients studied within 24 hours after the onset of acute myocardial infarction. To provide a common basis for comparison the mean arterial pressure was lowered to the same level of about 80 mmHg in the previously normotensive patients and 90 to 100 mmHg in the patients with a history of hypertension, respectively. To provide a direct comparison in the same patients, of 20 patients treated with nitroprusside, 12 were also treated with nitroglycerin; 8 patients were given nitroprusside as well as phentolamine.

Phentolamine produced a highly significant increase in cardiac index, stroke volume index, and heart rate. Overall nitroprusside did not produce significant changes of the same indices, but in patients with a cardiac index less than 2·5 l/min per m² an increase in cardiac index was noted. Glyceryl trinitrate, however, produced a significant decrease in cardiac index and stroke volume index.

Total systemic vascular resistance declined most during phentolamine administration, from 21·0 to 11·2 units, during nitroprusside from 21·8 to 15·2, and during glyceryl trinitrate from 19·9 to 17·4. Compared with nitroprusside, in the same subject, the greater effect of phentolamine, and the lesser one of glyceryl trinitrate, on the total systemic vascular resistance were statistically significant.

The ratio Δ per cent left ventricular filling pressure/Δ per cent systemic vascular resistance rose considerably with glyceryl trinitrate since a large decrease in left ventricular filling pressure was opposed by only a minor decrease of systemic vascular resistance. Phentolamine, because of its greater effect in decreasing systemic vascular resistance leads to a small decline in the ratio. Nitroprusside led to an increase in the ratio Δ per cent left ventricular filling pressure/Δ per cent systemic vascular resistance which fell between the effects of the other two agents, but which was closer to the effect of phentolamine.

The results indicate that nitroprusside had the most beneficial effect in the patients studied. Vasodilator therapy for acute myocardial infarction, however, should be limited to patients with high blood pressure and/or pump failure and pulmonary congestion until its local effect on the acute ischaemic myocardium is better understood.

Several reports have been published on the treatment of congestive heart failure or acute myocardial infarction with various vasodilator drugs (Gould *et al.*, 1969; Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973; Kelly *et al.*, 1973; Gould *et al.*, 1974; Walinsky *et al.*, 1974; Come *et al.*, 1975; da Luz *et al.*, 1975; von Leitner *et al.*, 1975; Williams *et al.*, 1975; Bussmann *et al.*, 1976; Miller *et al.*, 1976). Though the value of left ventricular unloading in improving cardiac performance is well documented, it is not known whether a given vasodilator agent has characteristic properties which are unique and which confer relative advantages in different clinical settings.

To our knowledge only one study has been performed to evaluate the characteristic properties of sodium nitroprusside, and glyceryl trinitrate by comparing the effects of these two agents on the same patient (Armstrong *et al.*, 1975). Accordingly, the present investigation was carried out to quantify and compare the effects of intravenous phentol-

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amine and nitroprusside, or nitroprusside and glyceryl trinitrate, respectively, with the mean arterial pressure lowered to and adjusted at an identical level in the same patient.

Methods

Twenty-nine patients between 26 and 80 years, mean age 62·3 years, were examined within 24 hours after the onset of symptoms of acute transmural myocardial infarction, documented by a typical history, electrocardiographic findings, and serum enzyme changes. The nature and purpose of the treatment and the associated studies were explained to each patient. Of the patients, 21 were men and 8 were women. The average time from the onset of symptoms to the first haemodynamic measurements was 10·25 ± 0·8 hours. Nineteen had anterior infarction and 10 had inferior myocardial infarction. Patients with rhythm disturbances were excluded from this study.

Pulmonary arterial catheterisation was performed at the bedside using a Swan-Ganz flow-directed balloon catheter[1] inserted percutaneously through the femoral vein. With gas sterilisation the catheters could be used 4 to 5 times. Cardiac output was determined by a thermodilution technique using injections of ice-cold 5 per cent glucose and a cardiac output computer.[2] The mean value of at least three measurements was computed; the stroke volume was derived using the heart rate counted each time. The pulmonary arterial pressure was measured through the same triple-lumen catheter. The arterial pressure was measured by means of a catheter introduced percutaneously from the femoral artery into the descending aorta. Mean pressures were obtained from an electronically integrated record. Recordings were made with a transportable ultraviolet light recorder.[3] Phasic pressure measurements were averaged over two whole respiratory cycles. The common zero reference level for all pressures was set at 5 cm below the sternal angle, with the patient supine. All measurements were made in the patient's room.

Measurements used to evaluate the cardiocirculatory changes included the following:

Stroke volume index (SVI) = stroke volume/body surface area (ml/m^2)

Systemic vascular resistance (SVR) = mean arterial pressure (MAP)/cardiac output (CO) (arbitrary units)

Mean per cent decrease in left ventricular filling pressure/mean per cent decrease in SVR ($\Delta\%$ LVFP/$\Delta\%$SVR), where LVFP = diastolic pulmonary arterial pressure.

Statistical analyses were performed using Student's t test with paired comparisons.

VASODILATOR THERAPY

Phentolamine, nitroprusside, and glyceryl trinitrate were administered intravenously by constant infusion pump[4] via a centrally placed venous catheter. Step by step increases in the dose were made at 3 to 5 minute intervals until a mean systemic arterial pressure of about 80 mmHg was reached. The infusion rate then was kept constant, or adjusted appropriately if necessary, to maintain a constant arterial pressure in the same patient. In 6 patients with known hypertension, the mean arterial pressure was lowered to 90 to 100 mmHg only. The average dosages needed were: phentolamine 1·34 mg/min (range, 0·4 to 5·0 mg/min); nitroprusside 88 µg/min (range, 33 to 273 µg/min); glyceryl trinitrate 50 µg/min (range, 8·3 to 117 µg/min).

Haemodynamic measurements were made 30 and 15 minutes before starting the drug infusion and repeated 15 and 30 minutes after the desired arterial blood pressure and a stable circulatory state had been obtained. There was always at least one hour without any vasodilator treatment between the administration of two different drugs for comparison. To make direct comparisons in the same subject 8 of 20 patients treated with nitroprusside also received phentolamine and 12 also received glyceryl trinitrate. Eight patients treated with phentolamine only and one patient treated with glyceryl trinitrate only were included for the better evaluation of the specific effect of each single drug. At the time of the study the patients were not receiving any other therapy.

Results

The results of direct comparisons in the same patients are summarised in Tables 1 and 2 and in Fig. 1 and 2. The combined results in all the patients investigated are summarised in Table 3 and in Fig. 3 and 4.

(1) LEFT VENTRICULAR FILLING PRESSURE (LVFP)

When directly compared in the same patient, nitroprusside was more effective in decreasing the filling pressure than phentolamine (Fig. 1, Table 1). Comparing nitroprusside and glyceryl trinitrate in the same patient, no difference could be shown (Fig. 2, Table 2). When all patients investigated were considered, the smaller effect of phentolamine

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[1] Model No. 93A-118-F: Edwards Laboratories Inc.

[2] Model 9510: Edwards Laboratories Inc.

[3] 5-127 recording oscillograph: Bell and Howell.

[4] Infusomat: Braun, Melsungen.

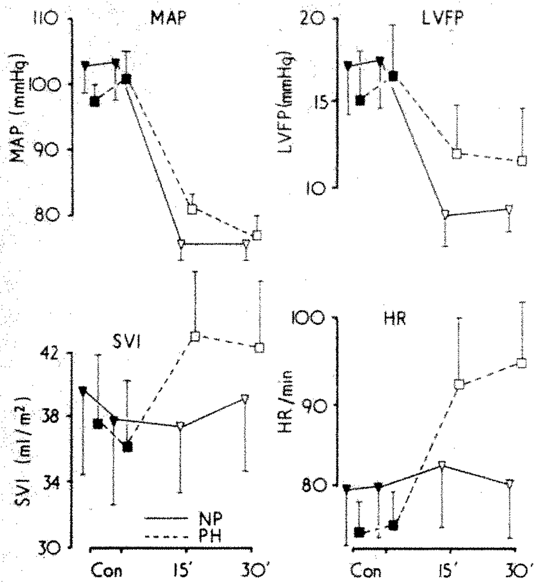

Fig. 1 *Comparison of the effects of phentolamine (PH) and sodium nitroprusside (NP) on haemodynamic variables in the same individuals (n=8). MAP, mean arterial pressure, SVI, stroke volume index; LVFP, left ventricular filling pressure; HR, heart rate. Closed symbols, control measurements 30 and 15 minutes before therapy. Open symbols, 15 and 30 minutes measurements after reaching the desired mean atrial blood pressure. (Means ± standard error of mean.)*

in decreasing the filling pressure was not apparent (Table 3, Fig. 4). This is because in those patients treated with nitroprusside in comparison with phentolamine, or treated with phentolamine only, the mean arterial pressure was generally lowered somewhat more.

(2) HEART RATE (HR)

During the infusion of glyceryl trinitrate or nitroprusside there was only a slight rise in heart rate. During administration of phentolamine, however, distinct increase in heart rate was observed (Table 3, Fig. 1).

(3) STROKE VOLUME INDEX (SVI)

On the average no significant change in stroke volume index was seen during infusion of nitroprusside. Phentolamine, however, produced significant increases in stroke volume index, which in all 16 patients investigated averaged 5·0 ml/m² ($P < 0 \cdot 001$). Glyceryl trinitrate, on the other hand, produced a significant decrease in stroke volume index from 35·2 ± 2·0 to 31·0 ± 1·9 ml/m² (Table 3) and a mean difference of 3 ml/m² when compared with the effect of nitroprusside in the same patient (Table 2).

(4) CARDIAC INDEX (CI)

In 20 patients nitroprusside caused only a small and nonsignificant increase of cardiac index. This increase was not dependent upon the initial left

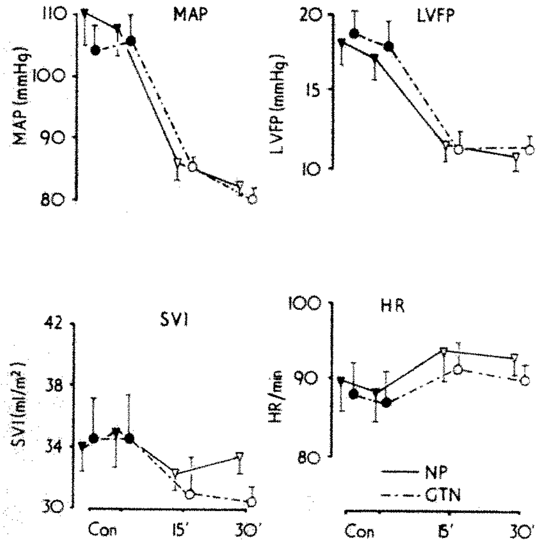

Fig. 2 *Comparison of the effects of sodium nitroprusside (NP) and glyceryl trinitrate (GTN) on haemodynamic variables in the same subjects (n=12). Abbreviations, etc., as in Fig. 1.*

Table 1 *Comparison of effects of sodium nitroprusside (NP) and phentolamine (PH) on haemodynamic variables in same individuals (n=8)*

	HR/min	*SBP (mmHg)*	*DBP (mmHg)*	*MAP (mmHg)*	*LVFP (mmHg)*	*CI (l/min per m²)*	*SVI (ml/m²)*	*SVR (units)*
C_{I}	80·3* ±5·7	139·6 ±6·4	80·4 ±5·2	102·6 ±7·0	17·3 ±3·0	3·0 ±0·35	39·5 ±5·0	22·0 ±3·4
C_{II}	80·5 ±5·9	145·3 ±7·0	80·9 ±6·2	103·0 ±6·6	17·5 ±2·9	2·9 ±0·36	37·6 ±5·0	23·2 ±3·4
$\mathrm{NP}_{15'}$	83·4 ±7·0	106·4 ±1·7	62·5 ±3·0	76·1 ±2·3	8·0 ±2·1	3·0 ±0·3	37·4 ±4·2	15·6 ±1·4
$\mathrm{NP}_{30'}$	81·1 ±5·6	106·4 ±2·6	61·9 ±3·0	76·0 ±2·7	8·5 ±1·4	3·1 ±0·3	39·2 ±3·8	15·1 ±1·5
$\mathrm{C}_{\mathrm{III}}$	75·4 ±3·5	138·4 ±2·8	75·3 ±3·2	96·9 ±3·1	14·8 ±3·0	2·7 ±0·26	37·2 ±4·7	22·4 ±2·7
C_{IV}	75·9 ±3·7	142·9 ±4·2	78·6 ±3·9	101·0 ±4·5	16·5 ±3·2	2·6 ±0·24	35·8 ±4·4	23·9 ±2·8
$\mathrm{PH}_{15'}$	93·3 ±7·7	120·0 ±5·4	61·5 ±3·6	80·8 ±3·2	11·8 ±3·1	3·8 ±0·29	43·4 ±4·8	12·8 ±1·3
$\mathrm{PH}_{30'}$	96·1 ±7·2	112·9 ±3·6	60·0 ±3·2	77·0 ±3·3	11·4 ±3·1	3·9 ±0·3	42·4 ±4·7	12·1 ±1·2
P values:								
C_{II}–C_{IV}	NS	NS	NS	NS	NS	NS	NS	NS
$\mathrm{NP}_{15'}$–$\mathrm{PH}_{15'}$	<0·05	<0·05	NS	<0·025	<0·025	<0·02	<0·025	<0·02
$\mathrm{NP}_{30'}$–$\mathrm{PH}_{30'}$	<0·025	NS	NS	NS	NS	<0·02	NS	<0·01

*All values represent means ±standard errors of the mean.
Abbreviations: C_{I} to C_{IV}, control measurements; $\mathrm{NP}_{15'}$ and $\mathrm{NP}_{30'}$; PH and $\mathrm{PH}_{15'}$, measurements 15 and 30 minutes after constant conditions had been obtained under nitroprusside infusion and phentolamine, respectively. HR, heart rate; SAP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LVFP, left ventricular filling pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance.

Table 2 *Comparison of effects of sodium nitroprusside (NP) and glyceryl trinitrate (GTN) on haemodynamic variables in same individuals (n=12)*

	HR/min	*SBP (mmHg)*	*DBP (mmHg)*	*MAP (mmHg)*	*LVFP (mmHg)*	*CI (l/min per m²)*	*SVI (ml/m²)*	*SVR (units)*
C_{I}	89·8* ±3·9	152·1 ±7·0	83·0 ±4·0	110·0 ±5·0	18·2 ±1·3	3·0 ±0·17	34·1 ±1·8	20·8 ±1·5
C_{II}	88·1 ±4·1	151·2 ±7·3	85·1 ±4·1	108·6 ±5·2	17·8 ±1·3	3·0 ±0·19	35·0 ±2·2	20·7 ±1·5
$\mathrm{NP}_{15'}$	93·7 ±3·2	119·5 ±3·7	70·4 ±2·6	86·4 ±3·2	11·7 ±1·2	3·1 ±0·16	32·6 ±1·8	16·3 ±1·0
$\mathrm{NP}_{30'}$	93·1 ±3·5	114·8 ±2·7	67·4 ±2·6	82·6 ±2·2	10·8 ±0·8	3·1 ±0·14	33·7 ±1·8	15·2 ±0·8
$\mathrm{C}_{\mathrm{III}}$	87·6 ±4·2	141·9 ±5·7	78·3 ±3·5	104·8 ±4·1	18·7 ±1·6	3·0 ±0·20	34·5 ±2·3	20·3 ±1·6
C_{IV}	87·9 ±3·7	146·2 ±7·7	79·3 ±3·8	105·4 ±5·1	18·5 ±1·5	3·0 ±0·17	35·3 ±2·3	19·9 ±1·4
$\mathrm{GTN}_{15'}$	91·3 ±3·9	114·1 ±2·8	70·2 ±2·2	85·1 ±1·7	11·5 ±1·1	2·8 ±0·14	31·3 ±2·2	17·5 ±1·2
$\mathrm{GTN}_{30'}$	90·5 ±3·8	111·4 ±3·0	67·3 ±2·7	80·3 ±2·2	11·3 ±1·1	2·7 ±0·14	30·6 ±1·8	17·3 ±1·2
P values								
C_{II}–C_{IV}	NS	NS	<0·005	NS	NS	NS	NS	NS
$\mathrm{NP}_{15'}$–$\mathrm{GTN}_{15'}$	NS	<0·02	NS	NS	NS	<0·025	NS	NS
$\mathrm{NP}_{30'}$–$\mathrm{GTN}_{30'}$	NS	NS	NS	NS	NS	<0·001	<0·005	<0·02

*All values represent means ±standard errors of the mean.
Abbreviations as for Table 1.

ventricular filling pressure before treatment (Fig. 3). It is possible that this effect was, however, related to the initial cardiac index, since the 5 patients with an index below 2·5 l/min per m² during therapy did show an increase in cardiac index. Phentolamine in all patients resulted in a highly significant increase in cardiac index, the average being 1·0 l/min per m². Glyceryl trinitrate infusion resulted in a significant decrease in the cardiac index, from an average of 3·0 ±0·1 to 2·8 ±0·1 l/min per m² (Table 3). These effects were not apparently dependent upon the initial filling pressure (Fig. 3). Compared with the same patients, the increase in cardiac index with phentolamine and the decrease with glyceryl

Table 3 *Summary of haemodynamic data of all patients: results after therapy in each patient are mean values of measurements after 15 and 30 minutes during constant conditions*

	HR/min	*SBP (mmHg)*	*DBP (mmHg)*	*MAP (mmHg)*	*LVFP (mmHg)*	*CI (l/min per m^2)*	*SVI (ml/m^2)*	*SVR (units)*
C	85·3*	148·0	82·9	105·6	18·1	2·9	35·6	21·8
	±3·5	±5·0	±3·4	±4·0	±1·4	±0·17	±2·4	±1·6
NP (n = 20)	88·6	110·0	65·1	79·70	10·3	3·1	35·4	15·2
	±3·3	±2·1	±1·7	±1·7	±0·9	±0·14	±2·0	±0·7
C	81·6	147·7	80·0	106·5	18·1	2·9	36·7	21·0
	±3·5	±4·9	±3·1	±4·3	±1·8	±0·14	±2·5	±1·7
PH (n = 16)	98·4	114·4	60·4	78·0	10·4	3·9	41·7	11·2
	±5·2	±4·1	±2·4	±2·0	±1·7	±0·14	±2·8	±0·7
C	88·0	146·6	80·0	105·6	18·6	3·0	35·2	19·9
	±3·4	±7·1	±3·5	±4·7	±1·4	±0·14	±2·0	±1·2
GTN (n = 13)	91·1	114·1	70·2	84·6	11·8	2·8	31·0	17·4
	±3·4	±2·5	±2·2	±1·7	±1·1	±0·14	±1·9	±1·3
P values								
C–NP	NS	< 0·001	< 0·001	< 0·001	< 0·001	NS	NS	< 0·001
C–PH	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001
C–GTN	NS	< 0·001	< 0·001	< 0·001	< 0·001	< 0·05	< 0·005	< 0·001

*All values represent means ± standard errors of the mean.
Abbreviations: C, control; NP, Na-nitroprusside; PH, phentolamine; GTN, glyceryl trinitrate.

trinitrate were significantly different from the overall lack of effect on cardiac index during nitroprusside infusion (Tables 1 and 2).

(5) RATIO Δ%LVFP/Δ%SVR

All three agents lowered the systemic vascular resistance, the greatest effect being the decrease during phentolamine infusion (from 21·0 ± 1·7 to 11·2 ± 0·7), and the least with glyceryl trinitrate (from 19·9 ± 1·2 to 17·4 ± 1·3) (Table 3).

Use of the ratio Δ%LVFP/Δ%SVR, relating the percentage reduction in filling pressure to that of vascular resistance allows comparison of the results obtained in all patients investigated. Administration of glyceryl trinitrate yielded a high value, since a pronounced decrease in filling pressure was associated with only a minor decrease in vascular resistance. By contrast, phentolamine, because of the distinct decrease in vascular resistance, yielded only a small decrease in the ratio. The effect of nitroprusside occupied an intermediate position but closer to that of phentolamine than that of glyceryl trinitrate (Fig. 4).

Discussion

The dramatic circulatory response to vasodilator agents and the experimental evidence that such therapy may reduce infarct size (Shell *et al.*, 1973) have led to the suggestion that vasodilator therapy might represent rational treatment for all patients with acute myocardial infarction. This investigation examines the contrasting effects on cardiac performance, on the peripheral resistance, and on vascular capacitance of the three commonly employed ventricular unloading agents phentolamine, sodium nitroprusside, and glyceryl trinitrate. In order to have a common basis for comparison in each individual patient, the mean arterial pressure was brought to the same level of about 80 mmHg in the previously normotensive patients and of 90 to 100 mmHg in patients with a history of hypertension, respectively.

Phentolamine administration in all patients resulted in a pronounced increase in cardiac index and stroke volume index (Table 3 and Fig. 3). The heart rate also rose significantly. Since such changes could be detected in only a few patients when identical reductions in the arterial pressure had been produced by infusion of nitroprusside or glyceryl trinitrate, these effects of phentolamine cannot be based only on the decrease in the afterload, or be explained simply by reflex mechanisms. Apparently, phentolamine possesses a positive inotropic and chronotropic effect independent of the lowering of the arterial pressure. Though the greatest reduction in peripheral resistance was produced by phentolamine, which should result in a greater reduction of impedance to the left ventricular ejection, and be expected to allow better systolic emptying, the increase in cardiac index and heart rate did not seem to follow the reduction of arterial pressure. Furthermore, as found by Gould *et al.* (1969), in some patients we observed that with small doses of phentolamine the decrease in the peripheral resistance was balanced by increases of stroke volume index and heart rate, so that reduction in the blood pressure could only be achieved by larger doses of phentolamine, or by the addition of small doses of practolol (von Leitner *et al.*, 1975).

Accordingly, the doses used by us (an average of 1·34 mg/min) seem to be relatively high but have also been reported by other authors (Miller *et al.*, 1976).

Experimental animal studies have suggested that a cardiac stimulatory effect of phentolamine is mediated via catecholamines (Dairman *et al.*, 1968; Bagwell *et al.*, 1970; Singh *et al.*, 1970), though Chatterjee *et al.* (1973) have doubted this mechanism. The authors referred to could not observe any positive inotropic effect of phentolamine in the isolated cat muscle. Increases of cardiac index with phentolamine have been found in patients with congestive heart failure with or without infarction (Gould *et al.*, 1969; Majid *et al.*, 1971; Perret *et al.*, 1975; Miller *et al.*, 1976), in patients with myocardial infarction and hypertension (Kelly *et al.*, 1973), and with normotensive blood pressure (Gould *et al.*, 1974). Walinsky *et al.* (1974), however, noted an increase of cardiac index only in patients with myocardial infarction and a left ventricular filling pressure above 15 mmHg. In our study we could not detect any dependence of phentolamine effect upon filling pressure (Fig. 3). The arteriolar vasodilating effect of phentolamine is caused by direct relaxing effect upon the smooth vascular muscle (Taylor *et al.*, 1965). The ratio Δ%LVFP/Δ%SVR shows that the influence of phentolamine on the arterioles clearly predominates when compared with its effect on the venous capacitance (Fig. 4).

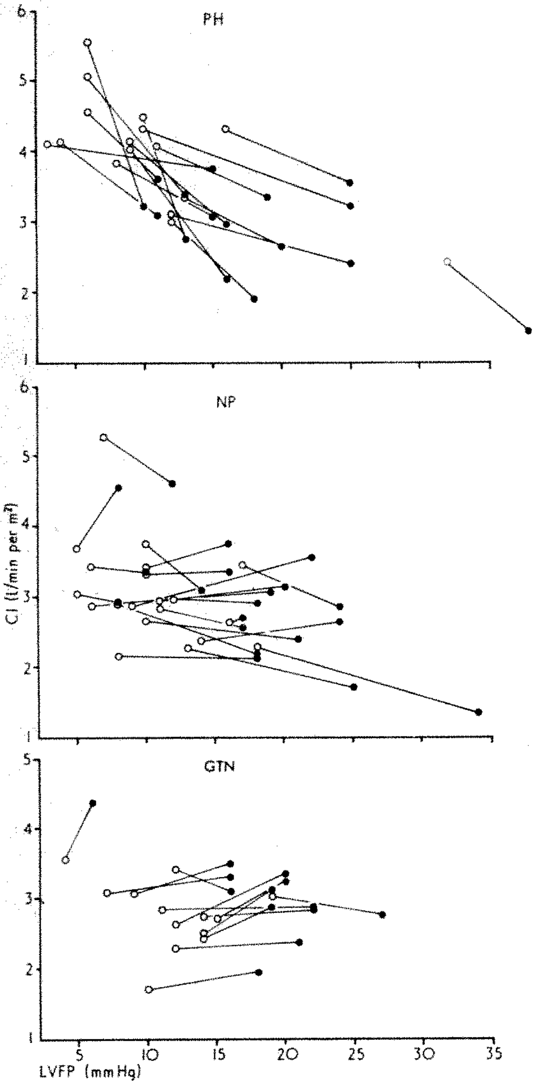

Fig. 3 *Effects of phentolamine (PH), sodium nitroprusside (NP), and glyceryl trinitrate (GTN) on cardiac index (CI) and left ventricular filling pressure (LVFP) of all patients investigated. Individual patients are indicated by a line connecting a closed circle (control) with an open circle (under therapy).*

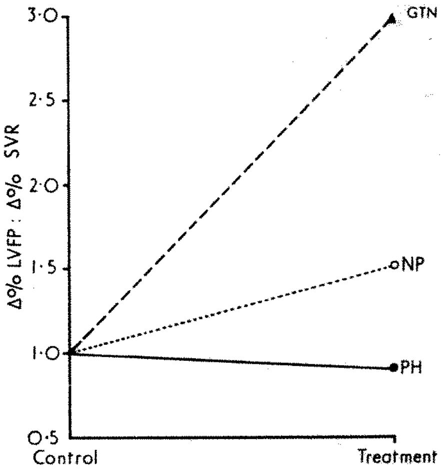

Fig. 4 *Effects of phentolamine (PH), sodium nitroprusside (NP), and glyceryl trinitrate (GTN) on the ratio of percentage change in left ventricular filling pressure (Δ%LVFP) to percentage change in systemic vascular resistance (Δ%SVR).*

Sodium nitroprusside caused a small, nonsignificant increase of the mean value of cardiac index with no change in the stroke volume. No clear relation between changes of cardiac index and the left ventricular filling pressure was apparent (Fig. 3). Likewise, changes in the cardiac index were not related to the filling pressure achieved under treatment. An unchanged stroke volume index despite a much decreased filling pressure implies a shift of the cardiac function curve to the left, which most probably results from the reduction of impedance to left ventricular outflow.

With vasodilator therapy, significant increase of the cardiac index in patients with severe congestive heart failure without infarction has been reported (Guiha *et al.*, 1974; Froer *et al.*, 1976; Kovick *et al.*, 1976). Increase in cardiac output in normotensive patients with infarction, low cardiac index, and lung oedema has also been observed (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1976). We can confirm this observation in some patients investigated with a low cardiac index. In keeping with our results, Franciosa *et al.* (1972) did not find any increase of cardiac index in patients with myocardial infarction who had a cardiac index above 2·5 l/min per m^2 before treatment.

Compared with phentolamine, nitroprusside produced a distinctly smaller effect on the peripheral arteriolar resistance; the comparatively greater reduction of left ventricular filling pressure, as a result of the more pronounced effect on the venous capacitance, led to a significant increase of the ratio $\Delta\%$LVFP/$\Delta\%$SVR (Fig. 4). The greater influence of nitroprusside on the venous capacitance became obvious in the direct comparison in the same patient, since at identical lowering of the arterial pressure the left ventricular filling pressure was lowered significantly more by nitroprusside than by phentolamine (Table 1, Fig. 1).

Glyceryl trinitrate, in our study, produced a significant decrease in stroke volume and cardiac index, even if left ventricular filling pressure was raised (Fig. 3, Tables 2 and 3). This is consistent with the findings in other studies (Come *et al.*, 1975; Flaherty *et al.*, 1976) which have shown, in acute myocardial infarction, a reduction of cardiac index during intravenous administration of glyceryl trinitrate, independent of the presence and severity of left ventricular failure. Similar results were reported by Williams *et al.* (1975) after sublingual administration of glyceryl trinitrate. Armstrong *et al.* (1975) did not find any significant changes in the cardiac index, whereas Bussmann *et al.* (1976) and Gold *et al.* (1972) described increases of cardiac index in patients with a high left ventricular filling pressure. The patients of Gold *et al.* (1972), however, were investigated within one week after acute myocardial infarction and Bussmann *et al.* (1976) did not specify exactly the time of their study in relation to the occurrence of infarction. In our patients, studied within 24 hours of the onset of symptoms, six had a left ventricular filling pressure of more than 20 mmHg; only one showed a small increase of cardiac index. Compared with nitroprusside, glyceryl trinitrate lowered cardiac output probably as a consequence of the predominance of its preload-reducing action over its effect of reducing impedance (Fig. 4).

The mean dose of glyceryl trinitrate necessary to maintain the arterial pressure at the chosen level was 3 mg per hour. This is in keeping with the doses given by other authors (Armstrong *et al.*, 1975; Come *et al.*, 1975; Flaherty *et al.*, 1976). On account of the great variability of the dose necessary and to avoid wide swings of blood pressure, use of fixed infusion doses such as 6 mg per hour (Bussmann *et al.*, 1976) does not seem judicious to us. Cohen *et al.* (1973), Flaherty *et al.* (1975), Armstrong *et al.* (1975), and Miller *et al.* (1976) found that glyceryl trinitrate affects the vascular capacitance more than the vascular resistance. The ratio $\Delta\%$LVFP/$\Delta\%$SVR in our patients confirmed these observations (Fig. 4). Of the three vasodilator drugs, glyceryl trinitrate had the least effect on the peripheral resistance. On the other hand, there was a distinct reduction of left ventricular filling pressure. According to Williams *et al.* (1975), falls of blood pressure produced by glyceryl trinitrate are mainly the result of a reduction of cardiac index. Only with higher doses does the lowering of systemic vascular resistance become more important (Flaherty *et al.*, 1976).

THERAPEUTIC IMPLICATIONS

In patients with pump failure complicating acute myocardial infarction a primary aim of treatment is to increase cardiac output while reducing left ventricular filling pressure. On this basis phentolamine seems to be the drug of first choice in such patients. On the other hand, one major object of vasodilatory therapy in this situation is to limit the extent of tissue damage during the process of acute myocardial infarction. That implies augmenting cardiac index only to the extent just needed for a sufficient nutritional flow to the periphery. Increases in cardiac index to nearly 4 l/min per m^2 as a mean value in several patients imply an overstimulation of the heart by phentolamine. In a study evaluating salvage of ischaemic myocardium by infusion of phentolamine for up to 48 hours, in most patients, we had to give practolol 10 mg i.v. several times in order to lower cardiac index and/or heart rate (von Leitner *et al.*, 1975).

In this study, within 24 hours after the onset of symptoms of acute myocardial infarction, glyceryl trinitrate reduced cardiac output, even in patients with a raised left ventricular filling pressure of more than 20 mmHg. Glyceryl trinitrate seems best suited for clinical application in the setting of severely raised filling pressure occurring concomitantly with preservation of normal cardiac output and arterial blood pressure. Without an initial rise of filling pressure pronounced decrease in ventricular preload at the expense of cardiac output may result in profound systemic hypotension (Williams *et al.*, 1975). Unintentional overtreatment with nitroprusside can quickly be reversed by stopping or slowing the infusion rate, whereas glyceryl trinitrate has a longer lasting effect.

During nitroprusside infusion in the present investigation cardiac index and stroke volume index remained in a range which provided an adequate nutritional blood flow. Even with a fall in filling pressure to a range of 5 to 10 mmHg the cardiac index and stroke volume index did not decline significantly and never to a critical amount. In patients with severe left ventricular failure intravenous nitroprusside usually improves the haemodynamic performance and considerably lowers the hospital mortality (Chatterjee *et al.*, 1976). These results point to nitroprusside being optimally beneficial in the commonly encountered clinical situation. Whether phentolamine may be superior in severe cardiac failure because of its inotropic effect is not known. It seems desirable to widen the clinical experience with both drugs in patients with severe cardiac failure.

Although vasodilators improve haemodynamic performance, their effect on the acutely ischaemic myocardium is not well established. The reduction in preload and in afterload should lead to a diminution in the myocardial oxygen consumption requirements. Recently, Chatterjee *et al.* (1973) and Kötter *et al.* (1976) have reported a significant fall in myocardial oxygen consumption in acute myocardial infarction during the infusion of phentolamine, nitroprusside, and glyceryl trinitrate, respectively. This most probably has to be regarded as a beneficial effect in relation to reduced cardiac work.

It does not seem possible that the improved cardiac performance produced by vasodilator therapy could occur if it was accompanied by a deleterious effect on the overall myocardial oxygen metabolism as a result of lowered coronary perfusion pressure. However, the possibility of increased hypoxia in some areas of the myocardium because of reduction in local perfusion pressure still cannot be ruled out. In experimental animal studies, vasodilators have given variable results; however, the basic principle which is emerging is that the perfusion pressure to the ischaemic zone must be maintained. Conflicting results have also been obtained from clinical studies. Chiariello *et al.* (1976), for example, suggest that glyceryl trinitrate reduced ischaemic injury by increasing perfusion of the ischaemic areas, whereas nitroprusside may increase ischaemia. These reported results, however, still have to be confirmed. From the above and our own experience it seems that for clinical practice today no method sensitive enough to prove a beneficial effect on the ultimate infarct size is yet available (Schröder, 1976; Schröder *et al.*, 1976). This difficulty, at least in part, may explain the contradictory results reported. At the present state of knowledge it seems advisable to us to limit vasodilator therapy in acute myocardial infarction to patients with raised arterial blood pressure and/or pump failure and pulmonary congestion until further studies have produced categorical evidence of beneficial effects in patients with uncomplicated myocardial infarction. Haemodynamic monitoring is not only essential for the selection of patients likely to benefit from such treatment but is also necessary to avoid complications such as an unexpected fall in arterial pressure.

References

Armstrong, P. W., Walker, D. C., Burton, J. R., and Parker, J. O. (1975). Vasodilator therapy in acute myocardial infarction. *Circulation*, **52**, 1118–1122.

Bagwell, E. E., Hilliard, C. C., Daniell, H. B., Taylor, P. L., and Walton, R. P. (1970). Studies on the inotropic mechanism of phentolamine (abstract). *American Journal of Cardiology*, **25**, 83.

Bussmann, W.-D., Schöfer, H., and Kaltenbach, M. (1976). Wirkung von Nitroglycerin beim akuten Myokardinfarkt. II. Intravenöse Dauerinfusion von Nitroglycerin bei Patienten mit und ohne Linksinsuffizienz und ihre Auswirkungen auf die Infarktgrösse. *Deutsche medizinische Wochenschrift*, **101**, 642–648.

Chatterjee, K., Parmley, W. W., Ganz, W., Forrester, J., Walinsky, P., Crexells, C., and Swan, H. J. C. (1973). Hemodynamic and metabolic responses to vasodilator therapy in acute myocardial infarction. *Circulation*, **48**, 1183–1193.

Chatterjee, K., Swan, H. J. C., Kaushik, V. S., Jobin, G., Magnusson, P., and Forrester, J. S. (1976). Effect of vasodilator therapy for severe pump failure in acute myocardial infarction on short-term and late prognosis. *Circulation*, **53**, 797–802.

Chiariello, M., Gold, H. K., Leinbach, R. C., Davis, M. A., and Maroko, P. R. (1976). Comparison between effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. *Circulation*, **54**, 766–773.

Cohen, M. V., Downey, J. M., Sonnenblick, E. H., and Kirk, E. S. (1973). The effects of nitroglycerin on coronary collaterals and myocardial contractility. *Journal of Clinical Investigation*, **52**, 2836–2847.

Come, P. C., Flaherty, J. T., Baird, M. G., Rouleau, J. R., Weisfeldt, M. L., Greene, H. L., Becker, L., and Pitt, B. (1975). Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction. *New England Journal of Medicine*, **293**, 1003–1007.

Dairman, W., Gordon, R., Spector, S., Sjoerdsma, A., and Udenfriend, S. (1968). Effect of α-blockers on catecholamine biosynthesis (abstract). *Federation Proceedings*, **27**, 240.

Da Luz, P. L., Forrester, J. S., Wyatt, H. L., Tyberg, J. V., Chagrasulis, R., Parmley, W. W., and Swan, H. J. C. (1975). Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium. *Circulation,* **52,** 400–407.

Flaherty, J. T., Come, P. C., Baird, M. G., Rouleau, J., Taylor, D. R., Weisfeldt, M. L., Greene, H., L. Becker, L. C., and Pitt, B. (1976). Effects of intravenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction. *British Heart Journal,* **38,** 612–621.

Flaherty, J. T., Reid, P. R., Kelly, D. T., Taylor, D. R., Weisfeldt, M. L., and Pitt, B. (1975). Intravenous nitroglycerin in acute myocardial infarction. *Circulation,* **51,** 132–139.

Franciosa, J. A., Guiha, N. H., Limas, C. J., Rodriguera, E., and Cohn, J. N. (1972). Improved left ventricular function during nitroprusside infusion in acute myocardial infarction. *Lancet,* **1,** 650–654.

Froer, K., Hall, D., Goppel, L., and Rudolph, W. (1976). Vasodilatatorische Therapie der chronischen Herzinsuffizienz. *Verhandlungen der Deutschen Gesellschaft für innere Medizin,* 1117–1119.

Gold, H. K., Leinbach, R. C., and Sanders, Ch. A. (1972). Use of sublingual nitroglycerin in congestive failure following acute myocardial infarction. *Circulation,* **46,** 839–845.

Gould, L., Reddy, C. V. R., Kalanithi, P., Espina, L., and Gomprecht, R. F. (1974). Use of phentolamine in acute myocardial infarction. *American Heart Journal,* **88,** 144–148.

Gould, L., Zahir, M., and Ettinger, S. (1969). Phentolamine and cardiovascular performance. *British Heart Journal,* **31,** 154–162.

Guiha, N. H., Cohn, J. N., Mikulic, E., Franciosa, J. A., and Limas, C. J. (1974). Treatment of refractory heart failure with infusion of nitroprusside. *New England Journal of Medicine,* **291,** 587–592.

Kelly, D. T., Delgado, C. E., Taylor, D. R., Pitt, B., and Ross, R. S. (1973). Use of phentolamine in acute myocardial infarction associated with hypertension and left ventricular failure. *Circulation,* **47,** 729–735.

Kötter, V., v. Leitner, E. R., Wunderlich, J., and Schröder, R. (1976). Wirkungsvergleich von Phentolamin (Regitin), Natriumnitroprussid (Nipride) und Nitroglycerin bei der Behandlung des akuten Herzinfarktes. *Intensivmedizin,* **13,** Suppl. 1, R. 52.

Kovick, R. B., Tillisch, J. H., Berens, S. C., Bramowitz, A. D., and Shine, K. I. (1976). Vasodilator therapy for chronic left ventricular failure. *Circulation,* **53,** 322–328.

Majid, P. A., Sharma, B., and Taylor, S. H. (1971). Phentolamine for vasodilator treatment of severe heart-failure. *Lancet,* **2,** 719–724.

Miller, R. R., Vismara, L. A., Williams, D. O., Amsterdam, E. A., and Mason, D. T. (1976). Pharmacological mechanisms for left ventricular unloading in clinical congestive heart failure. Differential effects of nitroprusside, phentolamine, and nitroglycerin on cardiac function and peripheral circulation. *Circulation Research,* **39,** 127–132.

Perret, Cl., Gardaz, J.-P., Reynaert, M., Grimbert, F., and Enrico, J.-F. (1975). Phentolamine for vasodilator therapy in left ventricular failure complicating acute myocardial infarction. *British Heart Journal,* **37,** 640–646.

Schröder, R. (1976). Rettung ischämischen Myokardgewebes beim Menschen? *Intensivmedizin,* **13,** Suppl. 1, R. 5.

Schröder, R., Kötter, V., and von Leitner, E.-R. (1976). Attempt to prove salvage of ischemic myocardium in acute myocardial infarction. In *7th Congress of Cardiology, 20–25 July 1976, Amsterdam,* Abstract book 1, 490.

Shell, W. E., Lavelle, J. F., Covell, J. W., and Sobel, B. E. (1973). Early estimation of myocardial damage in conscious dogs and patients with evolving myocardial infarction. *Journal of Clinical Investigation,* **52,** 2579–2590.

Singh, J. B., Hood, W. B., and Abelmann, W. H. (1970). Beta adrenergic mediated inotropic and chronotropic actions of phentolamine (abstract). *American Journal of Cardiology,* **26,** 660.

Taylor, S. H., Sutherland, G. R., MacKenzie, G. J., Staunton, H. P., and Donald, K. W. (1965). The circulatory effects of intravenous phentolamine in man. *Circulation,* **31,** 741–754.

von Leitner, E. R., Kötter, V., and Schröder, R. (1975). Beeinflussung der Infarktgrösse durch Senkung der Herzarbeit bei akutem Myokardinfarkt. *Zeitschrift für Kardiologie,* Suppl. II, 58.

Walinsky, P., Chatterjee, K., Forrester, J., Parmley, W. W., and Swan, H. J. C. (1974). Enhanced left ventricular performance with phentolamine in acute myocardial infarction. *American Journal of Cardiology,* **33,** 37–41.

Williams, D. O., Amsterdam, E. A., and Mason, D. T. (1975). Hemodynamic effects of nitroglycerin in acute myocardial infarction: decrease in ventricular preload at the expense of cardiac output. *Circulation,* **51,** 421–427.

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Metabolic and hormonal studies in patients with essential hypertension

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In 106 patients with essential hypertension and different plasma renin activity several hormonal and metabolic factors were studied: urinary excretion of catecholamines, blood levels of cholesterol and triglycerides, levels of glycaemia and insulinaemia after glucose load and plasma fibrinolytic activity. The plasma renin activity in 46·2 per cent of patients was normal, whereas in 25·5 per cent it was low, and in 28·3 per cent it was high. In patients with high plasma renin activity the excretion of noradrenaline and adrenaline was relatively high while that of dopamine was low. Significantly lower triglyceride levels were found in patients with low plasma renin activity in comparison with those with high and normal plasma renin activity. There was also a statistically significant difference in the euglobulin lysis time which was shortest in patients with low and longest in patients with normal plasma renin activity. The results of the study show that patients with different plasma renin activity may also differ in some hormonal and metabolic values.

It has been shown recently that patients with essential hypertension do not represent a homogeneous population in relation to humoral factors (Brunner *et al.*, 1972; DeQuattro and Miura, 1973; Laragh, 1973; Januszewicz and Wocial, 1975). Particular attention has been paid to the observation that patients with essential hypertension differ in relation to plasma renin activity. It was found that the activity of this enzyme was normal in about 50 to 60 per cent of patients, while in others it was low or high (Brunner *et al.*, 1972; Crane *et al.*, 1972). Brunner *et al.* (1972, 1973) suggested that patients with different plasma renin activity differed also in relation to the clinical course of hypertension and the incidence of cardiovascular complications. Though this interesting observation was not confirmed by other authors (Doyle *et al.*, 1973; Mroczek *et al.*, 1973) it gave an impetus for further research to elucidate the relation between humoral factors and the clinical course of essential hypertension.

The aim of the present work was to investigate some metabolic and hormonal factors in patients with essential hypertension and different plasma renin activity.

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Patients and methods

The investigations were carried out in 106 patients with essential hypertension, 41 women and 65 men, aged 19 to 59 years. The diagnosis of essential hypertension was based on the clinical picture and special laboratory tests and radiological methods to exclude secondary forms of hypertension. All patients were in hospital and remained on a standard diet. They did not receive any hypotensive drugs and other drugs which might have influenced the values for at least 3 weeks before the study.

Plasma renin activity was measured by radioimmunoassay of angiotensin I using CEA-IRE-SORIN kits. The patients were divided into 3 groups on the basis of plasma renin activity; the arithmetic mean of plasma renin activity obtained in the control group of 20 healthy people ± 1 SD was accepted as a criterion of division; 49 patients (46%) were defined as having normal plasma renin activity, 27 patients (26%) had low, and 30 patients (28%) had high plasma renin activity. The mean age in all groups was similar. The known duration of hypertension was 7·4 years in the normal renin group and 5·2 and 5·6 years in the low and high renin groups, respectively. The mean haematocrit values were 43·9 ±4·2 in the normal renin group, 44·4 ±3·6 in the low renin group, and 44·3 ±4·1 in the high renin group and they did not show statistical differences.

The basic data related to the 3 groups of patients are presented in the Table.

In all patients the following investigations were done: (1) urinary excretion of noradrenaline and adrenaline according to the method of Von Euler and Lishajko (1961) and urinary excretion of dopamine according to Carlsson and Waldeck (1958); (2) serum levels of cholesterol using the method of Theorell (Cramer and Isaksson, 1959) and triglyceride using the enzymatic method with Boehringer tests; (3) plasma immunoreactive insulin levels and glucose tolerance test after oral glucose load (Somogyi, 1952); (4) fibrinolytic activity measured by dilute blood clot lysis time (Fearnley *et al.*, 1957) and euglobulin lysis time (Niewiarowski, 1960).

The results were statistically evaluated using Student's t test; the accepted level of significance was $P < 0.05$.

Results

The urinary excretion of noradrenaline and adrenaline was lowest in patients with low plasma renin activity (Fig. 1). The highest noradrenaline excretion was seen in patients with high plasma renin activity. The differences in noradrenaline excretion between high renin and normal renin groups as well as between high renin and low renin groups were statistically significant. There was also a statistically significant difference between adrenaline in high and low renin groups. In comparison with the control group, a statistically significant difference in urinary noradrenaline excretion was seen only in patients with low plasma renin activity. The differences in urinary excretion of adrenaline between patients and controls were not significant.

In contrast to the noradrenaline excretion, the urinary excretion of dopamine was highest in the low renin group and lowest in the high renin group. The differences were statistically significant (Fig. 2). The dopamine excretion was significantly lower in patients with normal and high plasma renin activity than in the control group.

The level of triglycerides was significantly lower in patients with low plasma renin activity in comparison with the remaining groups, while the level of cholesterol was the highest in patients with normal plasma renin activity (Fig. 3). It should be noted that both triglyceride and cholesterol levels

Table *106 patients with essential hypertension (41 women, 65 men) age 19–59 years*

	Normal PRA	Low PRA	High PRA
No. of cases	49 (46%)	27 (26%)	30 (28%)
Mean age (y)	36·6	38·1	36·3
Mean plasma renin activity (ng/ml per h)	2·3 ±0·97	0·2 ±0·06	6·3 ±4·81

PRA, plasma renin activity.

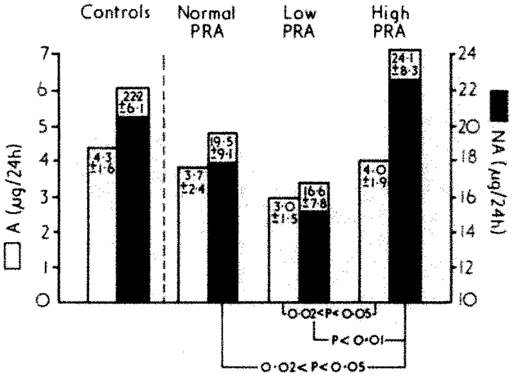

Fig. 1 *Mean urinary adrenaline (A) and noradrenaline (NA) excretion.*

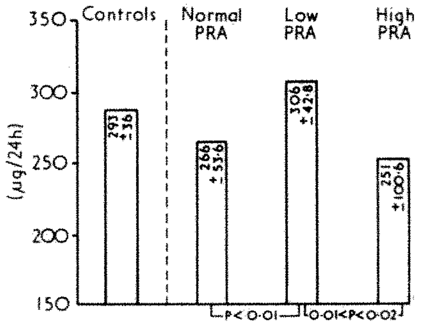

Fig. 2 *Mean urinary dopamine excretion.*

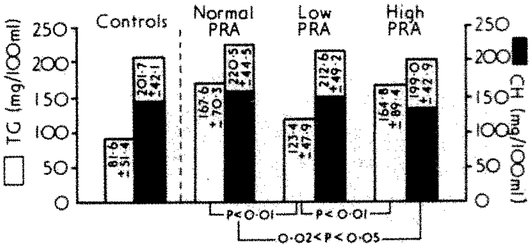

Fig. 3 *Mean serum triglyceride (TG) and cholesterol (CH) levels.*

in all groups of patients were significantly higher than in the controls.

The mean values of fasting glucose did not differ significantly between the investigated groups of patients and the controls. However, there was a difference in the shape of the glycaemic curves; in patients with normal and low plasma renin activity the levels of glucose were statistically higher than in controls beginning 1½ hours after the glucose load, while in patients with high plasma renin activity a significant difference was found after ½ hour and later.

The fasting level of glucose in patients with low plasma renin activity was statistically lower than in patients with normal plasma renin activity ($P < 0{\cdot}05$). One hour after the glucose load glycaemia was significantly higher in patients with high plasma renin activity than in those with normal ($P < 0{\cdot}01$) and low ($P < 0{\cdot}02$) plasma renin activity (Fig. 4).

The fasting plasma immunoreactive insulin levels of patients with hypertension did not differ significantly from those of the controls. However, after the glucose load there was a significant difference between the patients and controls: in the normal plasma renin activity group—after 1½, 2, and 2½ hours, in the low plasma renin activity group—after 1½ hours and later, and in the high plasma renin activity group after ½, 1, 1½, and 2 hours.

The differences between the groups of patients with hypertension were statistically significant only 1 hour after the glucose load (Fig. 5).

Fig. 6 shows the results of dilute blood clot lysis time and euglobulin lysis time in the investigated groups of patients. Difference in euglobulin lysis time between low and normal plasma renin activity groups was statistically significant. In comparison with the control group, there were no significant differences in relation to dilute blood clot lysis time, while the euglobulin lysis time was significantly longer in patients with normal plasma renin activity than in controls.

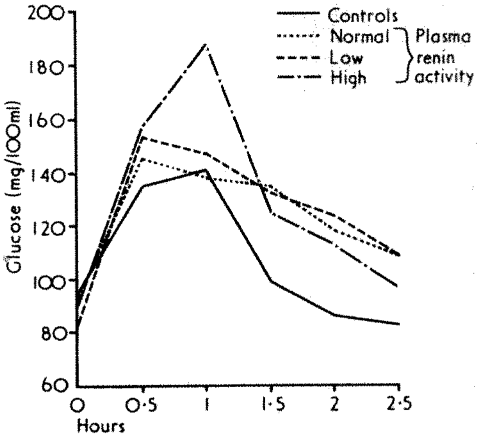

Fig. 4 *Oral glucose tolerance test.*

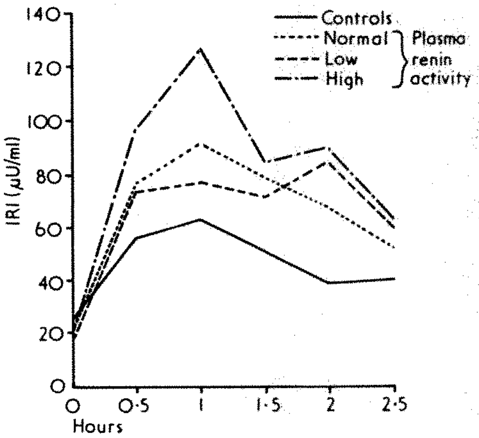

Fig. 5 *Plasma immunoreactive insulin levels (IRI) after glucose load.*

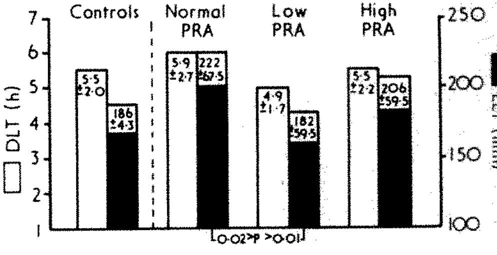

Fig. 6 *Fibrinolytic activity measured by dilute blood clot lysis time (DLT) and euglobin lysis time (ELT).*

Discussion

The results obtained in this study show that patients with essential hypertension and different plasma renin activity also show different hormonal and metabolic patterns. The question arises as to whether those differences may contribute to the clinical picture and the course of the disease. In the light of the complex nature of essential hypertension the answer to this question is not simple. However, it seems that some explanations may be suggested.

The differences in noradrenaline excretion may confirm the relation between the renin-angiotensin system and the sympatho-adrenal activity. Such a relation was suggested by various authors on the basis of experimental and clinical observations (Vander, 1965; Wathen *et al.*, 1965; Michelakis *et al.*, 1969; DeQuattro and Miura, 1973). Our results are in agreement with the observations of DeQuattro *et al.* (1975) who found a much higher percentage of hypertensive patients with raised catecholamine levels in the high renin group in comparison with groups of patients with low and normal plasma renin activity.

The differences in dopamine excretion are also interesting in view of the physiological properties of this amine. It is noteworthy that some authors observed the inverse relation between renin activity and dopamine excretion in certain physiological conditions connected with increased sympathetic activity (Cuche *et al.*, 1974).

The high glucose and insulin levels in patients with high plasma renin activity may be related to the raised catecholamine secretion in these patients, which may be responsible both for the increase of endogenous insulin secretion and for impaired action of this hormone resulting in abnormal carbohydrate tolerance.

The differences in triglyceride levels and fibrinolytic activity between groups of patients with different plasma renin activity deserve special attention. The prolongation of euglobulin lysis time in patients with normal and high plasma renin activity in comparison with low renin group is related to higher triglyceride levels in these groups. It is known that the pre-β-lipoprotein fraction rich in endogenous triglycerides inhibits the plasminogen activator secretion in the blood vessel wall and its deficiency may cause inhibition of fibrinolysis (Spöttl *et al.*, 1968). Both triglyceride increase and fibrinolysis inhibition may promote the development of atherosclerotic changes in blood vessels. It should be added that in patients with ischaemic heart disease the incidence of hypertriglyceridaemia and inhibition of fibrinolytic system is similar (Chakrabarti *et al.*, 1968).

On the basis of the results of the study it is possible that the metabolic changes seen in patients with different plasma renin activity may be one of the factors responsible for the varying incidence of cardiovascular complications in these patients. However, in the light of present knowledge it is difficult to assess whether these differences are related to the pathogenetic heterogeneity of essential hypertension and whether they may influence the natural history of the disease.

This investigation was partially supported by Polish Academy of Sciences, Dep. VI.

References

Brunner, H. R., Laragh, J. H., Baer, L., Newton, M. A., Goodwin, F. T., Krakoff, L. R., Bard, R. H., and Bühler, F. R. (1972). Essential hypertension: renin and aldosterone, heart attack and stroke. *New England Journal of Medicine*, **286**, 441–449.

Brunner, H. R., Sealey, J. E., and Laragh, J. H. (1973). Renin sub-groups in essential hypertension: further analysis of their pathophysiological and epidemiological characteristics. *Circulation Research*, **32–33**, Suppl. I, 99–105.

Carlsson, A., and Waldeck, B. (1958). A fluorometric method for the determination of dopamine (3-hydroxytyramine). *Acta Physiologica Scandinavica*, **44**, 293–298.

Chakrabarti, R., Hocking, E. D., Fearnley, G. R., Mann, R. D., Attwell, T. N., and Jackson, D. (1968). Fibrinolytic activity and coronary artery disease. *Lancet*, **1**, 987–990.

Cramer, K., and Isaksson, B. (1959). An evaluation of the Theorell method for the determination of total serum cholesterol. *Scandinavian Journal of Clinical and Laboratory Investigation*, **11**, 213–216.

Crane, M. G., Harris, J. J., and Johns, V. J. (1972). Hyporeninemic hypertension. *American Journal of Medicine*, **52**, 457–466.

Cuche, J. L., Kuchel, O., Barbeau, A., Langlois, Y., Boucher, R., and Genest, J. (1974). Autonomic nervous system and benign essential hypertension in man: II. Circulatory and hormonal responses to upright posture. *Circulation Research*, **35**, 290–297.

DeQuattro, V., Campese, V., Miura, Y., and Meijer, D. (1975). Biochemical markers of sympathetic nerve activity and renin in primary hypertension. In *Pathophysiology and Management of Arterial Hypertension*, p. 23. Ed. by G. Berglund, L. Hansson, and L. Werkö. Lindgren and Söner AB. Mölndal, Sweden.

DeQuattro, V., and Miura, Y. (1973). Neurogenic factors in human hypertension: mechanism or myth? *American Journal of Medicine*, **55**, 362–378.

Doyle, A. E., Jerums, G., Johnston, C. I., and Louis, W. J. (1973). Plasma renin levels and vascular complications in hypertension. *British Medical Journal*, **2**, 206–207.

Fearnley, G. R., Balmforth, G., and Fearnley, E. (1957). Evidence of diurnal fibrinolytic rhythm. *Clinical Science*, **16**, 645–650.

Januszewicz, W., and Wocial, B. (1975). Dopa, catecholamines and their metabolites in essential hypertension. *Clinical Science and Molecular Medicine*, **48**, 295s–298s.

Laragh, J. H. (1973). Vasoconstriction—volume analysis for understanding and treating hypertension. The use of renin and aldosterone profiles. *American Journal of Medicine*, **55**, 261–274.

Michelakis, A. M., Caudle, J., and Liddle, G. W. (1969). *In vitro* stimulation of renin production by epinephrine, norepinephrine, and cyclic AMP. *Proceedings of the Society for Experimental Biology and Medicine*, **130**, 748–753.

Mroczek, W. J., Finnerty, F. A., and Catt, K. J. (1973). Lack of association between plasma-renin, and history of heart-attack or stroke in patients with essential hypertension. *Lancet*, **2**, 464–469.

Niewiarowski, S. (1960). *Krzepniecie krwi*. Pañstwowy Zakad Wydawn Lekarskich, Warsaw.

Somogyi, M. (1952). Notes on sugar determination. *Journal of Biological Chemistry*, **195**, 19–23.

Spöttl, F., Holzknecht, F., and Braunsteiner, H. (1968). Inhibitors of the plasminogen-activation in patients with primary "carbohydrate-induced" hypertriglyceridemia. *Journal of Atherosclerosis Research*, **8**, 821–826.

Vander, A. J. (1965). Effect of catecholamines, and the renal nerves on renin secretion in anesthetized dogs. *American Journal of Physiology*, **209**, 659–662.

Von Euler, U. S., and Lishajko, F. (1961). Improved technique for the fluorometric estimation of catecholamines. *Acta Physiologica Scandinavica*, **51**, 348–356.

Wathen, R. L., Kingsbury, W. S., Stouder, D. A., Schneider, E. G., and Rostorfer, H. H. (1965). Effects of infusion of catecholamines and angiotensin II on renin release in anesthetized dogs. *American Journal of Physiology*, **209**, 1012–1024.

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Effect of atenolol (ICI 66 082) on coronary haemodynamics in man

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The coronary haemodynamic effect of atenolol, a new cardioselective beta-adrenergic blocker, was studied in 15 patients with angina pectoris.

Myocardial blood flow from the anterolateral part of the left ventricle was measured by the continuous infusion thermodilution method by means of a two-thermistor catheter with pacing electrodes placed in the great cardiac vein. Catheters were also positioned in the pulmonary artery and the thoracic aorta for blood sampling, pressure measurements, and cardiac output determination. Investigations were performed at rest, at slow, and at submaximal atrial pacing rates before and 10 minutes after injection of 5 mg atenolol intravenously. Coronary angiography was performed in all patients.

Atenolol reduced resting myocardial blood flow by 16 per cent ($P<0{\cdot}001$) and oxygen consumption by 17 per cent ($P<0{\cdot}001$). Flow was reduced whether or not the part of myocardium in question was supplied by a stenotic artery. Coronary arteriolar resistance increased by 23 per cent ($P<0{\cdot}001$). Myocardial arteriovenous oxygen difference was not affected. Heart rate and rate-pressure index were reduced in all patients ($P<0{\cdot}001$). When the heart rate was kept constant by atrial pacing there was no change in the rate-pressure index and no change in any of the coronary haemodynamic values. A small but highly significant increase of 2 mmHg ± 0·4 (SEM) in left ventricular filling pressure was observed at rest ($P<0{\cdot}001$), and 4 mmHg ± 0·7 ($P=0{\cdot}001$) during submaximal pacing. In all three situations the flow per unit left ventricular pressure work was identical before and after atenolol.

It is concluded that the decrement in myocardial blood flow and oxygen consumption effected by the drug could be attributed solely to the reduction in left ventricular work. No direct effect on coronary resistance could be identified. By reducing left ventricular work atenolol will be effective in the treatment of ischaemic heart disease. Since it increases left ventricular filling pressure it must be used with care in patients with latent heart failure.

The beneficial effect of beta-adrenergic blockade in the treatment of angina pectoris is well documented, though the mode of action has been a matter of debate.

A new beta blocker, atenolol (ICI 66 082, 'Tenormin'), has recently been introduced. Preliminary animal studies have shown that it is a selective inhibitor of beta$_1$-receptors without intrinsic sympathomimetic or membrane stabilising effects. It is as potent as propranolol in antagonising the positive chronotropic response to isoprenaline and stimulation of the cardioaccelerator nerve in the cat, but is less effective in antagonising lipolysis in adipose tissue (Barrett *et al.*, 1973).

Clinical studies in patients with ischaemic heart disease have shown that atenolol reduces significantly the frequency of anginal attacks (Roy *et al.*, 1975). However, detailed information on its effects on cardiac function in man has not been available, The aim of this investigation was to test the effect of the drug on coronary haemodynamics at rest and at a submaximal stress test, in patients with angina pectoris.

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Subjects and methods

PATIENTS

Fifteen patients (1 woman and 14 men) with angina pectoris and without evidence of additional myocardial or valvular heart disease were studied, mean age 47 years ±7 (SD). All were sufficiently incapacitated by angina to warrant consideration for coronary bypass surgery. None of the subjects showed clinical signs of heart failure and the heart size was normal as judged by *x*-ray examination.

Three of the patients had only minor coronary pathology while the rest had significant (more than 50%) stenosis of at least one of the three main coronary arteries. Three patients had stenosis of 1, 4 of 2, and 5 of all 3 arteries. Eight patients had a normal left anterior descending artery, while 7 had a significant stenosis of this vessel. Left ventricular ejection fraction exceeded 50 per cent in all the patients. None of the patients was treated with beta-blocking agents and no other drugs were given during the 24 hours before the investigation. They were examined in the supine position after premedication with 0·1 g aprobarbitone. Informed consent was obtained from all the participants.

CATHETERISATION

A special preshaped 7 F two-thermistor thermodilution catheter with pacing electrodes was positioned in the great cardiac vein in the depth of the coronary sinus, through a left antecubital vein. The position was initially assessed by injection of a small amount of contrast material and controlled by fluoroscopy repeatedly throughout the investigation. A 7 F Cournand catheter was placed in the pulmonary artery and a polyethylene catheter inserted into the thoracic aorta.

MEASUREMENTS

Cardiac venous flow was measured by the continuous infusion thermodilution method (Ganz *et al.*, 1971). For this purpose a 0·9 per cent saline solution at room temperature was infused into the great cardiac vein with a Harvard infusion pump at a constant rate of 36 ml/min for 20 to 30 seconds. This method has been found to be reliable for determination of great cardiac venous blood flow in our laboratory with a mean difference between duplicate measurements performed within 1 minute of 3·6 per cent of mean flow (Simonsen, 1977). Pressures were measured by Elema—Schønander EMT 35 transducers and recorded on a Mingograph 800 ink-jet recorder. Ten consecutive beats were analysed and the average pressures were used. Mean pressures were obtained by electrical integration. Aortic stenosis was excluded at left ventricular catheterisation and systolic aortic pressure was, therefore, taken as left ventricular systolic pressure. Cardiac output was determined by the direct Fick method.

PROCEDURE

When all catheters were positioned the patient's angina threshold was tested. This was done by pacing from the cardiac vein, using a Medtronic external pacemaker, at a slowly increasing frequency until unmistakable angina was experienced by the patient. Then a period of complete rest of 15 minutes was allowed before the measurements were started. Cardiac venous flow was then measured at resting conditions, at a pacing frequency about 10 per minute above resting heart rate and at a submaximal rate 10 per minute below the rate producing angina pectoris. Blood samples were withdrawn from the cardiac vein and aorta immediately before each flow measurement while pressures were recorded simultaneously. Cardiac output was measured only at the two pacing procedures. Ten minutes after an injection of 5 mg atenolol had been given intravenously the complete procedure was repeated.

CALCULATIONS

Great cardiac venous blood flow was calculated from the formula

$$F_I \times 1{\cdot}19 \qquad \left(\frac{T_B - T_I}{T_B - T_M} - 1\right)$$

where T_B, T_I, and T_M represent the temperature of blood, injectate, and mixture of blood and injectate, respectively. F_I is the volume of injectate and 1·19 is a constant derived from the density and specific heat of saline solution and blood (Ganz *et al.*, 1971).

Myocardial oxygen consumption = (arterial cardiac venous oxygen content) × cardiac venous flow.

Heart rate pressure index = heart rate per min × peak systolic aortic pressure.

Left ventricular minute work =

$$\frac{CO\,(Ao - LVFP) \times 13{\cdot}6}{1000}$$

where CO is cardiac output, Ao is peak aortic pressure, and LVFP is left ventricular filling pressure (represented by the diastolic pulmonary arterial pressure).

Coronary arteriolar resistance = mean aortic pressure divided by cardiac venous flow.

Statistical analysis was performed using standard procedures. Student's t test for paired comparison was used when observations before were compared with those after atenolol. Differences were regarded as significant when $P < 0{\cdot}05$.

Results

The effect of atenolol on coronary haemodynamics is presented in Table 1 and that on general haemodynamics in Table 2.

OBSERVATIONS AT REST

A reduction in great cardiac venous blood flow

Table 1 *Coronary haemodynamic variables before and after 5 mg atenolol intravenously*

		Rest	*Slow pacing*	*Submaximal pacing*
Great cardiac venous blood flow (ml/min)	B	89 (10)	105 (12)	135 (15)
	A	75 (8)	109 (13)	132 (15)
		$P<0{\cdot}001$	NS	NS
Myocardial arteriovenous oxygen difference (%)	B	59 (1·9)	58 (1·5)	59 (1·3)
	A	60 (2·1)	58 (1·7)	59 (1·7)
		NS	NS	NS
Myocardial oxygen consumption (ml/min)	B	9·6 (0·9)	11·0 (1·1)	14·6 (1·5)
	A	8·0 (0·8)	11·4 (1·2)	14·0 (1·4)
		$P<0{\cdot}001$	NS	NS
Coronary arteriolar resistance (mmHg/ml per min)	B	1·3 (0·1)	1·2 (0·2)	1·0 (0·2)
	A	1·6 (0·2)	1·2 (0·1)	1·0 (0·1)
		$P=0{\cdot}001$	NS	NS
Flow/rate-pressure index $\times 10^{-3}$ (ml/mmHg–beats)	B	9·5 (1·2)	9·5 (1·1)	9·0 (1·1)
	A	9·2 (1·1)	9·8 (1·3)	9·0 (1·1)
		NS	NS	NS
Flow/left ventricular minute work (ml/g m)	B	—	9·2 (1·2)	10·0 (1·4)
	A	—	10·7 (1·3)	11·4 (1·5)
			NS	NS
Myocardial oxygen consumption/rate-pressure index $\times 10^{-4}$ (ml/mmHg-beats)	B	10·3 (1·2)	9·9 (1·1)	9·7 (1·1)
	A	10·0 (1·2)	10·3 (1·2)	9·5 (1·1)
		NS	NS	NS
Myocardial oxygen consumption/left ventricular minute work (ml/g m)	B	—	9·7 (1·2)	10·6 (1·5)
	A	—	11·5 (1·4)	12·1 (1·4)
			NS	NS

Mean values (±SEM) and the significance of differences are given. B, before; A, after; NS, not significant, i.e. $P>0{\cdot}05$.

Table 2 *General haemodynamic variables before and after 5 mg atenolol intravenously*

		Rest	*Slow pacing*	*Submaximal pacing*
Heart rate (beats/min)	B	74 (3)	82 (2)	110 (2)
	A	63 (3)	82 (2)	110 (2)
		$P<0{\cdot}001$	NS	NS
Systolic aortic pressure (mmHg)	B	133 (5)	137 (5)	140 (5)
	A	133 (5)	139 (5)	138 (5)
		NS	NS	NS
Diastolic pulmonary artery pressure (mmHg)	B	6 (0·4)	6 (0·5)	7 (0·7)
	A	8 (0·5)	9 (0·8)	11 (1·2)
		$P<0{\cdot}001$	$P=0{\cdot}002$	$P=0{\cdot}001$
Cardiac index (l/min)	B	—	3·6 (0·2)	3·8 (0·2)
	A	—	3·5 (0·2)	3·8 (0·2)
			NS	NS
Stroke volume (ml)	B	—	81 (3)	65 (3)
	A	—	80 (4)	64 (3)
			NS	NS
Rate-pressure index $\times 10^{-3}$ (mmHg-beats/min)	B	9·7 (0·4)	11·1 (0·3)	15·4 (0·7)
	A	8·3 (0·4)	11·3 (0·4)	15·2 (0·6)
		$P<0{\cdot}001$	NS	NS
Left ventricular minute work (g m)	B	—	11·8 (0·5)	12·6 (0·6)
	A	—	11·6 (0·7)	12·1 (0·7)
			NS	NS

Mean values (±SEM) and the significance of differences are given. B, before; A, after; NS, not significant, i.e. $P>0{\cdot}05$.

was noted in all patients averaging 16 per cent ($P<0{\cdot}001$). The mean reduction in flow was 18 per cent in the patients where the left anterior descending artery was normal compared with 12 per cent in those with stenosis of this vessel ($P>0{\cdot}05$). In 13 of the subjects the myocardial oxygen consumption was reduced. In 2, in whom only a very small reduction in blood flow took place, there was a minute increase in oxygen consumption caused by a small increase in arteriovenous oxygen difference. Overall there was a highly significant fall with a mean of 17 per cent ($P<0{\cdot}001$). Coronary arteriolar resistance increased by 23 per cent ($P<0{\cdot}001$) while the arteriovenous oxygen difference remained unchanged. Heart rate was reduced in all patients (mean 11 beats per min ($P<0{\cdot}001$)). Aortic systolic pressure did not change, but as a result of the fall in heart rate, the rate-pressure index was significantly reduced after atenolol ($P<0{\cdot}001$). The mean reduction in rate-pressure index was 21 per cent in the patients with normal, compared with 10 per cent in those with stenosed left anterior descending artery. Flow per unit rate-pressure index is, however, equal in the 2 groups. The individual changes

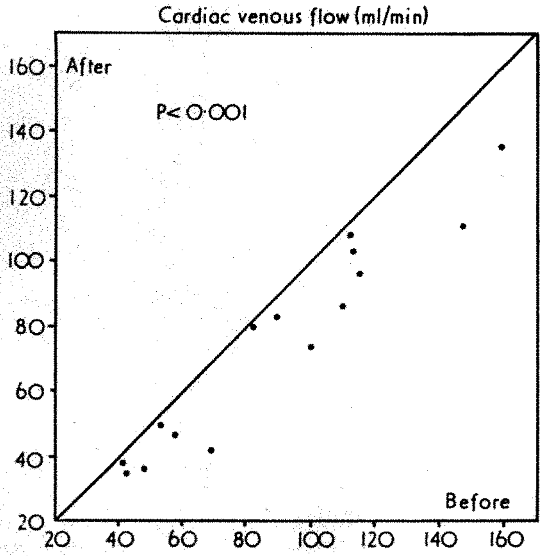

Fig. 1 *Cardiac venous flow before and after atenolol.*

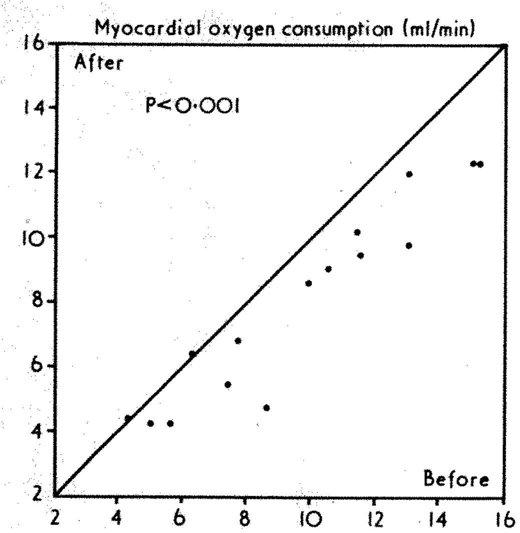

Fig. 2 *Myocardial oxygen consumption before and after atenolol.*

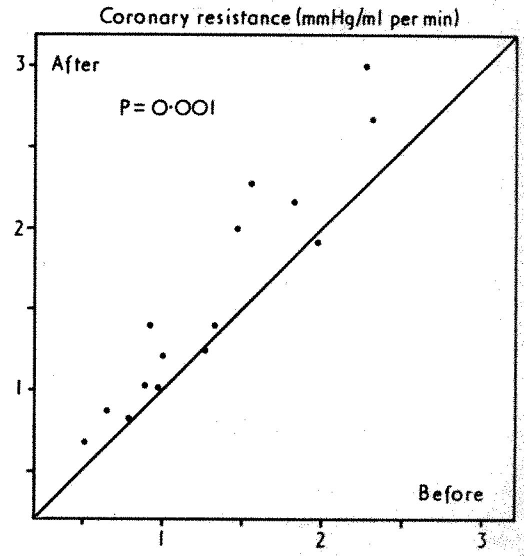

Fig. 3 *Coronary resistance before and after atenolol.*

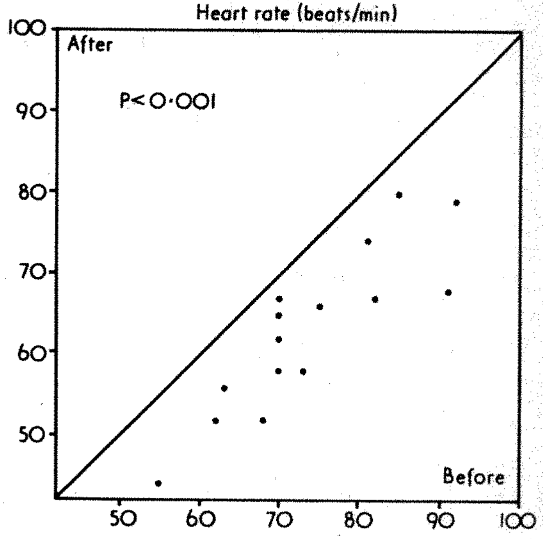

Fig. 4 *Heart rate before and after atenolol.*

in flow, myocardial oxygen consumption, coronary arteriolar resistance, heart rate, and rate pressure index for all the patients are graphically presented in Fig. 1 to 5. The diastolic pulmonary arterial pressure showed a mean increase of 2 mmHg ±0·4. Though numerically small the increase was consistent (Fig. 6) and statistically significant ($P < 0{\cdot}001$). The increase is, in the absence of mitral valvular disease, taken to represent an increase in left ventricular filling pressure. The relation between myocardial blood flow per unit work and oxygen consumption per unit work showed no significant change after atenolol.

OBSERVATIONS DURING ATRIAL PACING

Both at the slow and the submaximal pacing rates the coronary haemodynamic variables were constant. Atenolol did not significantly change myo-

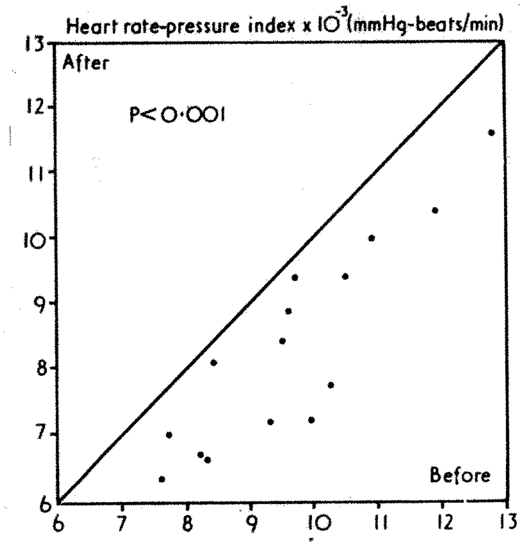

Fig. 5 *Heart rate pressure index before and after atenolol.*

cardial blood flow, oxygen consumption, or coronary arteriolar resistance. There was no difference in the effects on patients with and patients without stenosis of the left anterior descending artery. The general haemodynamic values showed only small changes. The same heart rate was obtained in all patients except one who at the submaximal pacing rate developed a second degree atrioventricular block after administration of the drug. He was, therefore, excluded from all calculations affected by this feature. Systolic aortic pressure, cardiac output, and the derived values for cardiac work, rate-pressure index, and left ventricular minute work, were not significantly altered. However, as at rest, there was a small but highly significant increase in diastolic pulmonary arterial pressure. At the slow pacing the increase was 2 mmHg $\pm 0{\cdot}6$ (SEM) ($P < 0{\cdot}001$) and at the submaximal pacing 4 mmHg $\pm 0{\cdot}7$ ($P = 0{\cdot}001$). The relation between myocardial blood flow (and oxygen consumption) and left ventricular work was unchanged by atenolol.

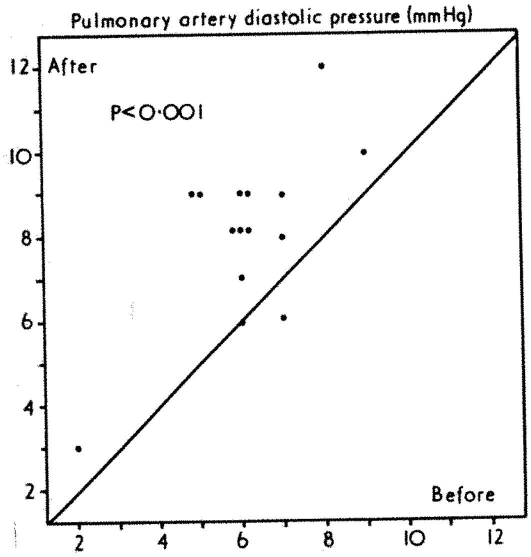

Fig. 6 *Pulmonary artery diastolic pressure before and after atenolol.*

Discussion

The present study has shown a reduction in myocardial blood flow and oxygen consumption and an increased coronary arteriolar resistance after atenolol. This supports previous work describing a reduction in flow after application of other selective (Moccetti *et al.*, 1972) as well as non-selective beta-adrenergic blockers (Wolfson *et al.*, 1966; Stein *et al.*, 1968; Mueller *et al.*, 1974). However, the opposite effect has also been described (Bussmann *et al.*, 1970).

The explanation for these findings must be sought among effects on determinants of myocardial oxygen consumption and possible direct effects on the coronary arteries.

The myocardial oxygen consumption at rest was reduced by atenolol parallel to a reduction in heart rate. By keeping the heart rate constant before and after the drug a stable haemodynamic state was achieved. There was no significant change in systolic aortic pressure and, therefore, the rate-pressure index remained unaltered. Thus, one of the main determinants of myocardial oxygen demand (Jørgensen *et al.*, 1973; Nelson *et al.*, 1974) was constant and oxygen consumption and myocardial blood flow remained unchanged. Considering blood flow and oxygen consumption per unit left ventricular work there was no change after atenolol in any of the 3 experimental situations. This shows that the mechanism responsible for the diminished blood flow at rest was probably a reduction in left ventricular work. Since the metabolic requirements of the myocardium were reduced, myocardial blood flow fell proportionately. This is in agreement with what has been previously shown for other beta-blockers in animal experiments (Stein *et al.*, 1968; Marchetti *et al.*, 1972) and in man (Wolfson and Gorlin, 1969). When, however, as shown in the present study, the work is increased again to pretreatment levels the flow increases in proportion.

The coronary arteriolar resistance at rest increased significantly after atenolol. The reduced flow could, therefore, be explained by an inhibition of sympathetic vasodilator tone as suggested for other beta-blockers (Klocke *et al.*, 1965; Parratt and Grayson, 1966). If this is a primary effect of the drug one would expect increased coronary arteriolar resistance and decreased flow also when myocardial oxygen demand is kept at the same level as before the beta-blockade. No change occurred after selective beta-blockade with atenolol under these circumstances. It has also been shown that the coronary arteries of the dog dilate to the same extent in response to temporary coronary occlusion before and after non-selective beta-blockade (Marchetti *et al.*, 1972). The present study shows that atenolol does not affect the ability of the human coronary arteries to dilate in response to an increase in myocardial oxygen demand. This is so both at low and submaximal levels of left ventricular work, and confirms an earlier study (Stephens *et al.*, 1976) in which atenolol was found not to give rise to coronary vasoconstriction. It has been shown (Pitt and Craven, 1970) that beta-blockade with propranolol alters the distribution of intramyocardial blood flow in the dog so that flow is selectively reduced to non-ischaemic areas. Other workers (Wolfson and Gorlin, 1969) have suggested that the action of propranolol in man may result in a more equitable distribution of coronary flow. This was assumed to occur if collateral vessels supplying ischaemic zones arose proximal to the arteriolar resistance bed and did not contain adrenergic receptors. Collaterals would then be given a selective advantage regarding perfusion when undiseased arterioles were constricted because of unopposed alpha effect after beta-blockade. The great cardiac vein drains the anterolateral left ventricular wall and the anterior part of the interventricular septum, in general the same area which gets its arterial supply through the left anterior descending artery. In the present study blood flow was reduced whether or not there was stenosis on this artery. There was, however, a smaller reduction in flow from the myocardium supplied by a stenotic artery. Flow per unit work was, however, equal in the two groups of patients. The smaller reduction in rate pressure index in the patients with left anterior descending artery stenosis seems, therefore, to be the most likely explanation for the difference in flow observed.

The increase in pulmonary arterial diastolic pressure after atenolol is presumed to reflect an increased left ventricular filling pressure. The drug may, therefore, increase ventricular wall tension and the diastolic volume of the heart as has been shown for other beta-blockers (Chamberlain, 1966; Swanton *et al.*, 1976) and thus increase myocardial oxygen demand (Simaan, 1974) which would tend to increase myocardial blood flow. Myocardial contractility was not measured in the present investigation, but has been shown to be decreased after atenolol (Stephan *et al.*, 1976) and this reduces oxygen consumption. These effects are small and probably balance one another since there is in all investigations a close relation between flow and pressure work.

The reduction in determinants of myocardial oxygen consumption seen in the present study after atenolol has also been seen during physical exercise (Åstrøm and Vallin, 1974). This explains why it is an effective antianginal drug. The effect on the left ventricular filling pressure indicates, however, that in common with all beta-adrenergic blocking agents, it must be used with care in patients with latent heart failure.

References

Åstrøm, H., and Vallin, H. (1974). Effect of a new beta-adrenergic blocking agent, ICI 66082, on exercise haemodynamics and airway resistance in angina pectoris. *British Heart Journal*, **36**, 1194–1200.

Barrett, A. M., Carter, J., Fitzgerald, J. D., Hull, R., and Le Count, D. (1973). A new type of cardioselective adrenoceptive blocking drug. *British Journal of Pharmacology*, **48**, 340P.

Bussmann, W. D., Rauh, M., and Krayenbuehl, H. P. (1970). Coronary and hemodynamic effects of myocardio-selective beta-receptor blockade by ICI 50172 in the closed-chest dog. *American Heart Journal*, **79**, 347–360.

Chamberlain, D. A. (1966). Effects of beta adrenergic blockade on heart size. *American Journal of Cardiology*, **18**, 321–328.

Ganz, W., Tamura, K., Marcus, H. S., Donoso, R., Yoshida, S., and Swan, H. J. C. (1971). Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation*, **44**, 181–195.

Jørgensen, C. R., Wang, K., Wang, Y., Gobel, F. L., Nelson, R. R., and Taylor, H. (1973). Effect of propranolol on myocardial oxygen consumption and its hemodynamic correlates during upright exercise. *Circulation*, **48**, 1173–1182.

Klocke, F. J., Kaiser, G. A., Ross, J., and Braunwald, E. (1965). An intrinsic adrenergic vasodilator mechanism in the coronary vascular bed of the dog. *Circulation Research*, **16**, 376–382.

Marchetti, G., Merlo, L., and Noseda, V. (1972). Mechanism of the decrease in coronary blood flow after beta-blockade in conscious dogs. *Cardiovascular Research*, **6**, 532–540.

Moccetti, T., Halter, J., and Lichtlen, P. (1972). Koronare und linksventrikuläre Dynamik dreier Substanzen mit unterschiedlicher β-blockierender Wirkung: Propranolol, Pindolol und Practolol. *Schweizerische medizinische Wochenschrift*, **102**, 422–425.

Mueller, H. S., Ayres, S. M., Religa, A., and Evans, R. G. (1974). Propranolol in the treatment of acute myocardial infarction. *Circulation*, **49**, 1078–1087.

Nelson, R. R., Gobel, F. L., Jørgensen, C. R., Wang, K., Wang, Y., and Taylor, H. L. (1974). Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation*, **50**, 1179–1189.

Parratt, J. R., and Grayson, J. (1966). Myocardial vascular reactivity after beta-adrenergic blockade. *Lancet*, **1**, 338–340.

Pitt, B., and Craven, P. (1970). Effect of propranolol on regional myocardial blood flow in acute ischaemia. *Cardiovascular Research*, **4**, 176–179.

Roy, P., Day, L., and Sowton, E. (1975). Effect of new β-adrenergic blocking agent, atenolol (Tenormin), on pain frequency, trinitrin consumption, and exercise ability. *British Medical Journal*, **3**, 195–197.

Simaan, J. (1974). Left ventricular volume as a determinant of myocardial oxygen consumption. *Cardiovascular Research*, **8**, 534–540.

Simonsen, S. (1977). Aspects on cardiac venous flow measured by the continuous infusion thermodilution technique. *Cardiology*, **62**, 51–62.

Stein, P. D., Brooks, H. L., Matson, J. L., and Hyland, J. W. (1968). Effect of beta-adrenergic blockade on coronary blood flow. *Cardiovascular Research*, **2**, 63–67.

Stephan, K., Abendroth, R.-R., Hubner, H., and Meesmann, W. (1976). Effects of the new β-adrenolytic agent atenolol on hemodynamics and contractility in normal hearts and on survival rate and arrhythmias after acute myocardial infarction. In *7th European Congress of Cardiology*, Abstract Book II, 99.

Stephens, J., Hamer, J., and Hayward, R. (1976). Effect of selective and non-selective beta-blockade on coronary circulation in man (abstract). *British Heart Journal*, **38**, 313.

Swanton, R. H., Grey, S., Arnold, V., Brooksby, I. A. B., Jenkins, B. S., and Webb-Peploe, M. M. (1976). Angina pectoris: effect of beta blockade on cardiac function, myocardial oxygen consumption and metabolites. In *7th European Congress of Cardiology*, Abstract Book II, 100.

Wolfson, S., and Gorlin, R. (1969). Cardiovascular pharmacology of propranolol in man. *Circulation*, **40**, 501–511.

Wolfson, S., Heinle, R. A., Herman, M. V., Kemp, H. G., Sullivan, J. M., and Gorlin, R. (1966). Propranolol and angina pectoris. *American Journal of Cardiology*, **18**, 345–352.

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Effect of testosterone cypionate on postexercise ST segment depression

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A randomised double blind study was carried out with 50 men who had ST segment depression of 0·1 mV or more after a modified two-step exercise test. Rate and duration of exercise were the same for the last of each subject's several pretreatment tests as for his tests after 4 and 8 weeks of treatment with placebo or testosterone cypionate, 200 mg, intramuscularly weekly. The sum of ST segment depression in leads II, V4, V5, and V6 taken immediately, and 2, 4, and 6 minutes after exercise did not change significantly after 4 or 8 weeks of placebo treatment, but did decrease by 32 per cent ($P<0\cdot0001$) and 51 per cent ($P<0\cdot0001$) after 4 and 8 weeks, respectively, of testosterone cypionate treatment. The mechanism by which testosterone cypionate treatment results in lessened postexercise ST segment depression is not established.

Premenopausal women have a lower incidence of myocardial infarction and death than men of similar age (Stamler, 1967). This observation has led to the notion that testosterone may predispose to, or that oestrogen may protect against, coronary artery disease. However, there has been no direct evidence linking testosterone administration to an increased incidence of myocardial infarction. On the contrary, it is oestrogen administration that has been associated with an increased incidence of myocardial infarction (Blackard *et al.*, 1970; Coronary Drug Project Research Group, 1970).

Recently, oestrogen administration has been found to increase ST segment depression in the postexercise electrocardiogram (Jaffe, 1976). Conversely, ethyloestrenol, an anabolic steroid, was found to lessen postexercise ST segment depression (Jaffe, 1973), and preliminary trials with testosterone cypionate[1] showed that this agent was particularly effective in this action. Therefore, the randomised double-blind study presented here was designed and carried out to test further the effect of testosterone cypionate therapy on the postexercise electrocardiogram.

Patients and methods

Fifty men were selected for this study from patients who had postexercise horizontal or downsloping ST segment depression of at least 1 mm (0·1 mV) in lead II, V4, V5, or V6 which had not been present in pre-exercise tracings. Subjects with evident valvular heart disease, symptoms or signs of cerebrovascular insufficiency or congestive heart failure, or electrocardiographic evidence of left ventricular hypertrophy, intraventricular conduction defect (QRS duration ≥0·12 second), or atrial fibrillation, and those receiving digitalis, quinidine, procainamide, or propranolol were excluded.

A two-step exercise test was used, employing a rate and duration of exercise for each subject that would result in postexercise ST segment depression. The two-step test was used for this study rather than a graded exercise test because we had had much prior experience in evaluating other therapeutic interventions using this test. Each subject performed at least three tests (not necessarily at the same workload) before he started treatment. The tests were carried out with the objectives of selecting subjects, establishing individual test workloads, and eliminating the possibility of improvement in exercise test performance resulting from a training effect. The last test before starting treatment was considered the baseline examination for comparison with subsequent tests in which exercise was performed at the same rate and for the same time as during the baseline examination.

A standard 12-lead resting electrocardiogram was taken before each exercise test. Leads II, V4, V5, and V6 were taken immediately, 2, 4, and 6 minutes after exercise, and at additional intervals as needed to observe the electrocardiogram until its return to the pre-exercise appearance. Brachial

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[1] Depotestosterone (Upjohn).

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cuff blood pressures were obtained with the subject in the supine position before exercise and immediately after exercise. Each test in a series was performed at about the same time of day and at least 4 hours postprandially. Every attempt was made to maintain exercise, work routine, food intake, and medication at a constant level throughout the study. However, because of the known effect of testosterone of causing fluid retention (Murad and Gilman, 1975), frusemide was administered to control fluid retention if, during the study, a subject gained 2·5 kg over pretreatment weight. For this reason 4 placebo treated and 9 testosterone cypionate treated subjects received frusemide for a mean duration of 2 weeks. 'Coronary vasodilator' drugs were discontinued 12 hours before each exercise test.

Before starting treatment, the nature of the study and possible effects and side-effects of cottonseed oil and of testosterone cypionate were thoroughly discussed with each subject and written informed consent was obtained.

Vials containing 10 ml of either cottonseed oil (placebo) or testosterone cypionate (200 mg/ml in cottonseed oil) which were identical in appearance except for a code number assigned by the Pharmacy Department of Bay Medical Center, where they had been prepared, were randomly assigned to the subjects. Each subject received 1 ml of either cottonseed oil or testosterone cypionate in cottonseed oil intramuscularly each week for 8 weeks. Neither the subject nor anyone involved in his medical care or testing learned which of the two materials was administered until after the study was completed. Records were kept of each subject's haemoglobin, haematocrit, and electrocardiographic response to exercise before treatment and after 4 and 8 weeks of treatment. Subjects were weighed weekly.

In each of 3 exercise tests (baseline, after 4, and after 8 weeks of treatment) for each subject the depression of the ST segment below the isoelectric line was measured at a locus 80 ms after the onset of the ST segment. Measurements were made in leads II, V4, V5, and V6 taken immediately, and 2, 4, and 6 minutes after exercise. The sum of these 16 measurements was used for comparing each baseline test with those performed after 4 and 8 weeks of treatment. [The severity of the ischaemic response may be graded not only by the magnitude of ST segment displacement, but also by its duration after the end of exercise (Bruce and Hornsten, 1969; Detry, 1973). Therefore the sum of the 16 measurements reflects both the magnitude and the duration of the ST segment depression in 4 leads, and may be a more representative assessment of the stress-induced abnormality than if only a single lead or time interval is employed.] The measurements were made from electrocardiographic tracings that were identified only by a numerical code that was unknown to the observer.

Results

Characteristics of the 50 men are shown in Table 1. Subjects ranged from 35 to 71 years in age, with a mean age of 58; 27 had earlier been found to have hypertension (diastolic pressure ≥ 90 mmHg); 10 had diabetes mellitus; 43 had stable, characteristic angina pectoris of at least 6 months' duration; and 20 had had a previous myocardial infarction confirmed by an abnormal Q-wave on electrocardiogram or by a clinical course (including cardiac enzyme changes) suggesting infarction. After the study was completed, the characteristics of the placebo and of the testosterone cypionate treated groups were tabulated (Table 1). There was no significant difference in any of the characteristics listed when they were analysed by the t test for the difference of means.

In the group treated with placebo for 4 weeks the sum of ST depression changed by mean ±SEM values of $-0{\cdot}4 \pm 0{\cdot}5$ mm and by $0{\cdot}6 \pm 2{\cdot}4$ per cent; and after 8 weeks by $-0{\cdot}2 \pm 0{\cdot}3$ mm and by $1{\cdot}6 \pm 2{\cdot}4$ per cent. None of these changes was significant when analysed by the paired t test (Table 2).

After 4 weeks of testosterone cypionate treatment the sum of ST depression decreased by mean ±SEM values of $3{\cdot}9 \pm 0{\cdot}9$ mm and by $31{\cdot}7 \pm 6{\cdot}5$ per cent; and after 8 weeks by $6{\cdot}0 \pm 1{\cdot}0$ mm and by $51{\cdot}2 \pm 7{\cdot}0$ per cent. All of these decreases were highly significant ($P < 0{\cdot}0001$) (Table 2).

Neither the mean haemoglobin level nor the mean haematocrit level changed significantly with 4 or 8 weeks of placebo treatment (Table 3). After 4 and 8 weeks of testosterone cypionate treatment, mean haemoglobin levels increased 0·7 and 1·4 g/100 ml, and mean haematocrit levels increased 3

Table 1 *Characteristics of the subjects*

	All subjects	*Placebo-treated subjects*	*Testosterone cypionate-treated subjects*
Number of subjects	50	25	25
Age range (y)	35–71	46–71	35–70
Mean age (y)	58	61	57
Hypertension	27	14	13
Diabetes mellitus	10	5	5
Angina pectoris	43	21	22
Previous myocardial infarction	20	10	10

and 5 ml/100 ml, respectively, all significant $(P < 0{\cdot}001)$ increases.

When subjects were grouped as placebo or testosterone cypionate treated, there was no significant change in weight, pre-exercise blood pressure, or immediate postexercise systolic pressure or heart rate after either 4 or 8 weeks of treatment (Table 3). However, when the testosterone cypionate treated subjects were subgrouped so that the first subgroup consisted of those whose change in ST segment

Table 2 *Comparison of sum of ST segment depression in leads II, V4, V5, and V6 before treatment (baseline) with values after 4 and 8 weeks of treatment with placebo or testosterone cypionate*

Subject No.	*Sum of ST depression*			*Change in sum of ST depression*			
	Baseline (mm)	*4 weeks (mm)*	*8 weeks (mm)*	*4 weeks (mm)*	*(%)*	*8 weeks (mm)*	*(%)*
Placebo treated							
1	14·7	14·2	12·4	−0·5	−3·4	−2·3	−15·6
2	40·2	30·1	34·3	−10·1	−25·1	−5·9	−14·7
3	10·2	10·5	8·9	0·3	2·9	−1·3	−12·7
4	12·3	14·1	10·9	1·8	14·6	−1·4	−11·4
5	29·0	23·2	25·8	−5·8	−20·0	−3·2	−11·0
6	14·2	13·8	13·1	−0·4	−2·8	−1·1	−7·7
7	10·9	9·8	10·2	−1·1	−10·1	−0·7	−6·4
8	3·5	3·6	3·3	0·1	2·9	−0·2	−6·1
9	5·2	4·8	4·9	−0·4	−7·7	−0·3	−5·8
10	11·0	11·3	10·5	0·3	2·7	−0·5	−4·5
11	9·0	8·2	9·0	−0·8	−8·9	0·0	0·0
12	6·8	6·7	6·8	−0·1	−1·5	0·0	0·0
13	14·9	16·1	15·2	1·2	8·0	0·3	2·0
14	10·8	10·3	11·2	−0·5	−4·6	0·4	3·7
15	15·4	15·9	16·0	0·5	3·2	0·6	3·9
16	7·4	7·5	8·0	0·1	1·3	0·6	8·1
17	9·8	9·4	10·7	−0·4	−4·1	0·9	9·2
18	6·3	6·2	7·0	−0·1	−1·6	0·7	11·1
19	12·6	13·4	14·0	0·8	6·3	1·4	11·1
20	7·0	7·9	7·8	0·9	12·9	0·8	11·4
21	7·3	9·4	8·2	2·1	28·8	0·9	12·3
22	10·3	9·2	11·6	−1·1	−10·7	1·3	12·6
23	10·1	10·3	11·5	0·2	2·0	1·4	13·9
24	9·5	10·3	10·9	0·8	8·4	1·4	14·7
25	11·3	13·8	13·7	2·5	22·1	2·4	21·2
Mean ±SEM	12·0 ±1·5	11·6 ±1·1	11·8 ±1·3	−0·4 ±0·5 P > 0·4	0·6 ±2·4 P > 0·7	−0·2 ±0·3 P > 0·5	1·6 ±2·4 P > 0·5
Testosterone cypionate treated							
1	7·0	0·0	0·0	−7·0	−100·0	−7·0	−100·0
2	4·9	1·2	0·0	−3·7	−75·5	−4·9	−100·0
3	13·8	0·8	0·7	−13·0	−94·2	−13·1	−94·9
4	3·3	3·4	0·2	0·1	3·0	−3·1	−93·9
5	5·0	3·2	0·8	−1·8	−36·0	−4·2	−84·0
6	15·9	9·0	3·7	−6·9	−43·4	−12·2	−76·7
7	8·3	3·6	2·0	−4·7	−56·6	−6·3	−75·9
8	10·1	4·9	2·5	−5·2	−51·5	−7·6	−75·2
9	8·2	5·5	2·1	−2·7	−32·9	−6·1	−74·4
10	10·0	3·4	3·2	−6·6	−66·0	−6·8	−68·0
11	20·9	10·6	6·9	−10·3	−49·3	−14·0	−67·0
12	10·1	9·8	3·5	−0·3	−3·0	−6·6	−65·3
13	8·2	2·8	3·7	−5·4	−65·8	−4·5	−54·9
14	44·9	28·6	21·8	−16·3	−36·3	−23·1	−51·4
15	11·8	8·3	6·3	−3·5	−29·7	−5·5	−50·8
16	9·0	6·6	5·6	−2·4	−26·7	−3·4	−37·8
17	20·3	17·6	13·7	−2·7	−13·3	−6·6	−32·5
18	29·7	23·3	22·8	−6·4	−21·5	−6·9	−23·2
19	15·4	13·9	12·3	−1·5	−9·7	−3·1	−20·1
20	12·6	12·8	10·2	0·2	1·6	−2·4	−18·0
21	11·3	11·0	9·9	−0·3	−2·6	−1·4	−12·4
22	12·1	13·3	11·2	1·2	9·9	−0·9	−7·4
23	10·5	9·8	9·9	−0·7	−6·7	−0·6	−5·7
24	7·0	7·3	6·7	0·3	4·3	−0·3	−4·3
25	10·5	11·3	12·0	0·8	7·6	1·5	14·3
Mean ±SEM	12·8 ±1·8	8·9 ±1·4	6·9 ±1·3	−3·9 ±0·9 P < 0·0001	−31·7 ±6·5 P < 0·0001	−6·0 ±1·0 P < 0·0001	−51·2 ±7·0 P < 0·0001

Table 3 *Results of treatment with placebo or with testosterone cypionate 200 mg/week (mean ±SEM)*

	Placebo treated N=25			*Testosterone cypionate treated N=25*			*Testosterone cypionate treated*			
							ST decreased > 50% N=15		*ST decreased < 50% N=10*	
	Baseline	*4 weeks*	*8 weeks*	*Baseline*	*4 weeks*	*8 weeks*	*Baseline*	*8 weeks*	*Baseline*	*8 weeks*
Haemoglobin (g/dl)	15·3 ±0·2	15·2 ±0·2	15·3 ±0·2	15·5 ±0·2	16·2 ±0·2*	16·9 ±0·2*	15·4 ±0·2	16·9 ±0·3*	15·7 ±0·2	16·8 ±0·3*
Haematocrit (ml/dl)	45 ±0·5	45 ±0·5	46 ±0·5	46 ±0·5	49 ±0·5*	51 ±0·5*	45 ±0·5	51 ±1·0*	47 ±0·5	51 ±1·0†
Weight (kg)	83 ±2·5	84 ±2·5	84 ±2·5	79 ±2·0	81 ±2·0	81 ±2·0	79 ±2·5	82 ±2·5	81 ±3·5	81 ±3·5
Pre-exercise BP (mmHg)	$\frac{134 \pm 4}{80 \pm 2}$	$\frac{132 \pm 4}{76 \pm 2}$	$\frac{133 \pm 4}{77 \pm 2}$	$\frac{135 \pm 4}{81 \pm 2}$	$\frac{133 \pm 4}{80 \pm 4}$	$\frac{135 \pm 4}{80 \pm 6}$	$\frac{130 \pm 4}{79 \pm 2}$	$\frac{132 \pm 4}{78 \pm 2}$	$\frac{142 \pm 7}{84 \pm 7}$	$\frac{139 \pm 6}{84 \pm 3}$
Postexercise systolic BP (mmHg)	166 ±4	168 ±6	166 ±6	172 ±5	168 ±5	167 ±6	174 ±6	166 ±8	169 ±9	168 ±11
Postexercise heart rate (beats/min)	132 ±4	134 ±4	134 ±4	138 ±4	135 ±4	134 ±4	135 ±6	129 ±6‡	142 ±5	141 ±4

Significantly different from baseline as determined by Student's t test.
*P < 001.
†P < 0·01.
‡ < 0·05.

depression at 8 weeks of treatment was greater than 50 per cent (i.e. the first 15 testosterone cypionate treated subjects listed in Table 2), and the second subgroup consisted of those whose ST segment depression was less than 50 per cent (i.e. the last 10 testosterone cypionate treated subjects listed in Table 2), then the subjects in the first subgroup experienced a significant (P < 0·05) decrease in postexercise heart rate. This was not found in the second subgroup (Table 3).

During the first 4-week treatment period 3 testosterone cypionate treated subjects received frusemide to control water retention. They showed a mean decrease in ST segment depression of 24·3 per cent as compared with a mean decrease of 32·3 per cent for the 22 testosterone cypionate treated subjects who received no frusemide during that time. Nine testosterone cypionate treated subjects who received frusemide during the second 4-week treatment period showed a mean decrease in ST segment depression of 53 per cent, whereas, the 16 testosterone cypionate treated subjects who received no frusemide during that time had a mean decrease of 50·2 per cent. This suggests that the effect of testosterone cypionate on postexercise ST segment depression was not significantly altered by adding frusemide.

Discussion

Although the placebo effect can have a strong and favourable influence on the symptoms of patients with angina pectoris (Dimond *et al.*, 1960), it has not been shown to affect electrocardiographic abnormalities after exercise. The lack of effect of placebo on the results of exercise testing is confirmed here by the lack of significant (P >0·7 and P >0·5) change in postexercise ST segment depression after 4 and 8 weeks of placebo treatment (Table 2).

In contrast, postexercise ST segment depression decreased by 31·7 per cent after 4 weeks of treatment with testosterone cypionate and by 51·2 per cent after 8 weeks of treatment, both decreases being highly significant (P < 0·0001).

There are many possible mechanisms by which testosterone cypionate treatment might result in decreased postexercise ST segment changes. For example, it might lessen postexercise ST segment abnormality by decreasing myocardial oxygen requirements. The immediate postexercise systolic blood pressure and the immediate postexercise heart rate reflect myocardial oxygen consumption. Neither was significantly decreased after testosterone cypionate treatment when statistical analysis dealt with the 25 testosterone cypionate treated subjects grouped together (Table 3). However, the subgroup consisting of the 15 testosterone cypionate treated subjects who developed a decrease in ST segment depression of greater than 50 per cent after 8 weeks of treatment experienced a mean postexercise heart rate which was significantly (P < 0·05) slower after treatment than before treatment (Table 3). This slower heart rate might be the cause of lessened ischaemia (consequent to decreased myocardial oxygen need) or it might be the result of lessened ischaemia. That is, myocardial ischaemia produces many changes in cardiac haemodynamics which might lead to an increased heart rate (Schlant, 1974). Therefore, lessened postexercise ischaemia might result in a slower postexercise heart rate. However, it is doubtful that a decrease in postexercise heart rate accounts for the decrease in postexercise ST segment depression after testosterone cypionate treatment because the change in the postexercise heart rate did not correlate with the change in the postexercise ST segment depression in these subjects ($r=0{\cdot}156$; $P=0{\cdot}6$).

Androgens increase red cell 2,3 diphosphoglycerate (Parker *et al.*, 1972) which may make oxygen more available to myocardial cells and which may inhibit platelet aggregation (Iatridis *et al.*, 1975) and may alter blood volume (Besa *et al.*, 1974). Testosterone produces a sense of increased physical vigour, increases skeletal muscle mass and strength, and causes retention of sodium, potassium, chloride, protein, and water (Murad and Gilman, 1975). These effects were not investigated in this study (except for recording subjects' weight).

An increased oxygen carrying capacity resulting from an increase in the blood haemoglobin level induced by testosterone cypionate treatment is another possible mechanism leading to lessening of postexercise ST segment abnormality. It is recognised (Shahidi, 1973) that haemoglobin levels rise in response to testosterone or anabolic steroid administration. In the present study mean haemoglobin values increased significantly ($P<0{\cdot}001$) after both 4 and 8 weeks of treatment with testosterone cypionate (Table 3). However, there was no significant correlation ($r=-0{\cdot}021$; $P>0{\cdot}9$) between changes in haemoglobin and postexercise ST segment depression in subjects treated with testosterone cypionate. This suggests that the decrease in mean postexercise ST segment depression after testosterone cypionate treatment probably results from a mechanism other than that of an increase in haemoglobin level.

Testosterone and anabolic steroids have been shown (Grunt and Higgins, 1960; Háva and Helfert, 1967; Greenberg *et al.*, 1973) to mediate a decrease in smooth muscle tone. An increase in coronary arterial smooth muscle mass secondary to sex hormone administration has been suggested (Jaffe and Rowe, 1972) as a mechanism for increasing coronary collateral development. Therefore, effects of testosterone on coronary arterial smooth muscle tone and/or mass may lead to dilatation of coronary arteries or their collaterals, and thereby decrease postexercise ST segment depression.

Testosterone might alter cell membrane properties or the distribution of ions to cause a change in the electrophysiology of the heart resulting in a lessening of postexercise ST segment depression. In the present study angina pectoris was not evaluated. However, in preliminary longer term studies the frequency and severity of angina pectoris decreased with testosterone cypionate treatment, suggesting that the decrease in ST segment depression may be related to lessened ischaemia rather than to altered electrophysiology.

This study shows that testosterone cypionate treatment results in lessened postexercise ST segment depression. The mechanism or mechanisms underlying this finding are unknown.

I am grateful to the many physicians who referred patients for this study and to Mary Lou Howell, for exercise testing; Louis Jacoby, for statistics; Donald Garvin, for helpful suggestions; and Park W. Willis, III, Ann Arbor, for review.

References

Besa, E. C., Gorshein, D., and Gardner, F. H. (1974). Androgens and human blood volume changes. *Archives of Internal Medicine,* **133,** 418–425.

Blackard, C. E., Doe, R. P., Mellinger, G. T., and Byar, D. P. (1970). Incidence of cardiovascular disease and death in patients receiving diethylstilbestrol for carcinoma of the prostate. *Cancer (Philadelphia),* **26,** 249–256.

Bruce, R. A., and Hornsten, T. R. (1969). Exercise stress testing in evaluation of patients with ischemic heart disease. *Progress in Cardiovascular Diseases,* **11,** 371–390.

Coronary Drug Project Research Group (1970). The coronary drug project. Initial findings leading to modifications of its research protocol. *Journal of the American Medical Association,* **214,** 1303–1313.

Detry, J. M. R. (1973). *Exercise Testing and Training in Coronary Heart Disease,* p. 19. Williams and Wilkins, Baltimore.

Dimond, E. G., Kittle, C. F., and Crockett, J. E. (1960). Comparison of internal mammary artery ligation and sham operation for angina pectoris. *American Journal of Cardiology,* **5,** 483–486.

Greenberg, S., Heitz, D. C., and Long, J. P. (1973). Testosterone-induced depression of adrenergic activity in the perfused canine hindlimb. *Proceedings of the Society for Experimental Biology and Medicine,* **142,** 883–888.

Grunt, J. A., and Higgins, J. T., Jr. (1960). Seminal vesicle response to androgen with adrenaline, noradrenaline and acetylcholine. *American Journal of Physiology,* **198,** 15–20.

Háva, M., and Helfert, I. (1967). Steroid blocking effect on smooth muscle contraction. *Archives Internationales de Pharmacodynamie et de Thérapie,* **166,** 79–86.

Iatridis, S. G., Iatridis, P. G., Markidou, S. G., and Ragatz, B. H. (1975). 2,3-Diphosphoglycerate: a physiological inhibitor of platelet aggregation. *Science,* **187,** 259–261.

Jaffe, M. D. (1973). Ethylestrenol, coronary artery disease and collaterals (abstract). *Clinical Research,* **21,** 813.

Jaffe, M. D. (1976). Effect of oestrogens on postexercise electrocardiogram. *British Heart Journal,* **38,** 1299–1303.

Jaffe, M. D., and Rowe, P. W. (1972). The mechanism by which female hormones enlarge collateral arteries. *Michigan Medicine,* **71,** 605–606.

Murad, F., and Gilman, A. G. (1975). Androgens and anabolic steroids. In *Pharmacological Basis of Therapeutics,* 5th ed., p. 1451. Ed. by L. S. Goodman and A. Gilman. Macmillan, New York.

British Heart Journal, 1977, **39**, 1223–1233

Pulmonary atresia with ventricular septal defect
Further anatomical observations

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An anatomical study was undertaken of 25 hearts with pulmonary atresia and ventricular septal defect, giving special attention to the morphology of the pulmonary outflow tract and the nature of the arterial supply to the lungs. A common feature of all hearts studied was the presence of sixth aortic arch derivatives within the pericardial cavity. Eighteen specimens presented with pulmonary atresia with ventricular septal defect in situs solitus, with atrioventricular concordance and normally related great arteries, that is with the pulmonary artery remnant anterior and to the left of the aorta. A blind or atretic pulmonary infundibulum was observed in all but one of these cases. In the remaining 7 specimens, the atretic pulmonary trunk was posterior to the aorta.

The pulmonary arterial blood supply was either through a ductus arteriosus or systemic-pulmonary anastomotic vessels. Anastomotic vessels were never observed together with a ductus, suggesting that the systemic-pulmonary vessels represent persistence of early arterial connections with the lungs when the ductus fails to develop.

The result of this study when compared with our previous studies indicates that a distinction can be made between pulmonary atresia with ventricular septal defect and persistent truncus arteriosus with absent pulmonary arteries ('type IV'). The latter is considered to be a true truncus arteriosus in which the arterial connections with the pulmonary vascular bed through the sixth aortic arches failed to develop, lack of septation of the cardiac outflow tracts rendering them superfluous, and thus only the early systemic-pulmonary connections persist. However, the condition is difficult or impossible to distinguish from pulmonary atresia with ventricular septal defect on clinical grounds.

In the examples of pulmonary atresia with ventricular septal defect and posteriorly placed pulmonary trunk remnants, the pulmonary circulation was always supplied by the ductus arteriosus; systemic-pulmonary arteries were never seen. The mechanism producing atresia of the posteriorly positioned pulmonary infundibulum seems to be different from the form with anteriorly placed pulmonary infundibulum, as no deviation of the conal septum was seen and the ventricular septal defect was rarely a malalignment defect.

Conflicting opinions exist concerning the classification, terminology, and precise nature of pulmonary atresia with ventricular septal defect. The wide variety of terms used to describe the malformation reflects this discordance of views as to its nature. Thus the anomaly has been termed truncus solitarius aorticus (Kugel, 1931), pulmonary atresia with biventricular aorta (Muñoz-Armas *et al.*, 1964), pseudotruncus arteriosus (Edwards *et al.*, 1965; Chesler *et al.*, 1970), extreme tetralogy of Fallot (Stuckey *et al.*, 1968), truncus arteriosus type IV (Taussig *et al.*, 1973), or has been described as single arterial trunk, aorta (Shinebourne *et al.*, 1976).

Since many examples of the anomaly have now undergone correction, it has been the subject of numerous clinical (Miller *et al.*, 1968; Somerville, 1970; Danilowicz and Ross, 1971; Jefferson *et al.*, 1972; Macartney *et al.*, 1973; Chesler *et al.*, 1974; Macartney *et al.*, 1974) and surgical reports (Ross and Somerville, 1966; McGoon *et al.*, 1970; Kouchoukos *et al.*, 1971; Doty *et al.*, 1972; Somerville and Ross, 1972; Berry *et al.*, 1974; Pacifico *et al.*, 1974; McGoon *et al.*, 1975; Marcelletti *et al.*, 1976). In contrast, few pathological investigations

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have been published (Muñoz-Armas *et al.*, 1964; Edwards and McGoon, 1973; Bharati *et al.*, 1975). It seemed that the anatomy of this cardiac defect had not yet been satisfactorily described. The present study was undertaken, specifically, to clarify the morphology of the ventricular outflow tracts and the arterial supply to the lungs.

Definition of terms

We define pulmonary atresia with ventricular septal defect as a malformation in which both ventricles eject into the aorta and in which some derivatives of the sixth aortic arches can be identified inside the pericardial cavity. When such derivatives are absent, we believe the anomaly to be a variant of persistent truncus arteriosus (Thiene *et al.*, 1976). In pulmonary atresia with ventricular septal defect there is a lack of continuity between the heart and the pulmonary artery and blood is supplied to the lungs by vessels derived from the aortic arch and the descending aorta. Twenty-five hearts from our collection showed these features.

Cases of pulmonary atresia with intact ventricular septum, atresia of an atrioventricular valve, common atrioventricular orifice, or primitive ventricle were excluded from this review.

The term 'transposition of the great arteries' has not been used throughout the paper to describe cases with anterior aorta and posterior atretic pulmonary trunk, because in this condition it is often impossible to determine if the pulmonary artery has indeed been placed across the septum (Shinebourne *et al.*, 1976).

Subjects and methods

The 25 anatomical specimens have been classified according to: visceroatrial situs; atrioventricular connections; cardiac position; and the spatial relation of the great arteries.

(a) SITUS SOLITUS (22 cases)

Eighteen cases presented with the classical features of pulmonary atresia with ventricular septal defect: laevocardia, concordant atrioventricular connection, and normally related great arteries, i.e. the atretic pulmonary artery was anterior and to the left of the aorta and potentially connected to the right ventricle. In contrast, 2 cases showed laevocardia, concordant atrioventricular connection, and single arterial trunk, but the atretic pulmonary artery was in a posterior position, being to the left of the aorta. The 2 remaining cases had the atretic pulmonary artery in the posterior position, but to the right of the aorta in association with atrioventricular discordance, one with laevocardia and the other with dextrocardia.

(b) SITUS INVERSUS (3 CASES)

Two hearts showed laevocardia, discordant atrioventricular connection, a posterior blind-ending pulmonary trunk, and an aorta to the right, while one presented with dextrocardia, concordant atrioventricular connection, a posterior blind-ending pulmonary artery, and an aorta to the left.

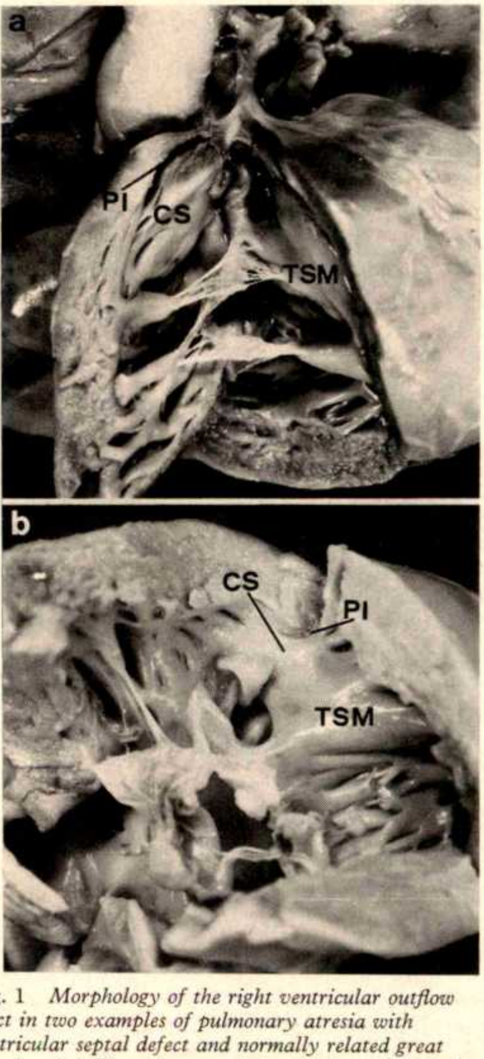

Fig. 1 *Morphology of the right ventricular outflow tract in two examples of pulmonary atresia with ventricular septal defect and normally related great arteries. (a) The pulmonary infundibulum (PI) is short and blind and the conal septum (CS) is anteriorly deviated and inserted behind the trabecula septomarginalis (TSM). (b) The pulmonary infundibulum is atretic from its origin.*

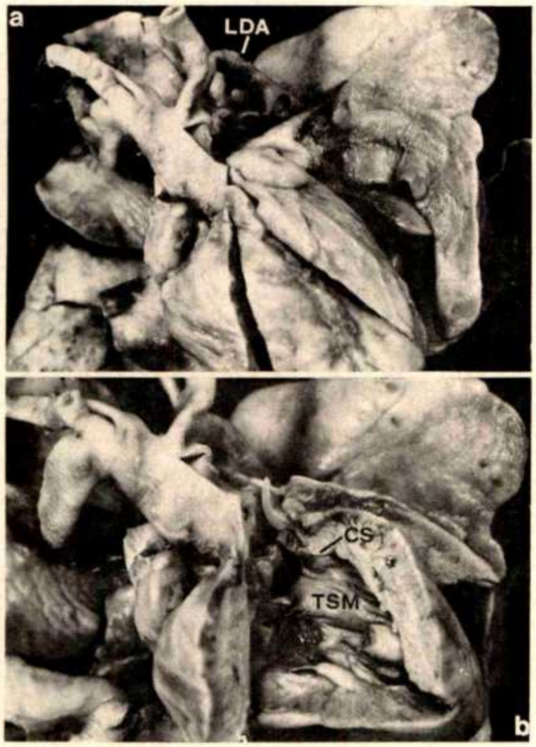

Fig. 2 *Morphology of the right ventricular outflow tract in pulmonary atresia with ventricular septal defect and no identifiable pulmonary trunk. (a) No pulmonary trunk is identifiable while a left ductus arteriosus (LDA) is connected with two confluent pulmonary arteries. The aortic arch is on the right side. (b) Right ventricular view: the conal septum (CS) is a distinct muscular structure fused with the base of the right ventricular free wall and inserted in front of the trabecula septomarginalis (TSM). The pulmonary infundibulum is completely atretic from its origin.*

All hearts were examined with specific attention to the morphology of the ventricular outflow tracts and the ventricular septal defect, arterioventricular alignment and aortic arch, coronary arterial patterns, systemic-pulmonary arterial supply, and size of the pulmonary trunk and its main branches.

Findings

After examining the hearts, the specimens were divided into 2 groups, on the basis of the *relation* of the great arteries, it being implicit in our definition that the ventriculoarterial connection was one of single arterial trunk.

Group 1 had the blind-ending pulmonary infundibulum or atretic pulmonary artery in the anterior position, so that the arterial relations were normal. Group 2, in contrast, had a posteriorly situated atretic pulmonary trunk.

GROUP 1: PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT AND NORMALLY RELATED GREAT ARTERIES (18 CASES)

(a) *Morphology of ventricular outflow tracts and ventricular septal defect*

In 13 hearts the pulmonary infundibulum was severely hypoplastic, anterior, and short, and the atresia was situated at valvular level (Fig. 1a). In 4 cases the pulmonary infundibulum appeared atretic from its origin: nevertheless the conal septum was identified as a distinct muscular structure fused with the anterior free wall of the right ventricle and the ventricular septum, in front of the trabecula septomarginalis (Fig. 1b). In one of these specimens, despite careful gross and histological examination, no pulmonary trunk was recognisable, while 2 confluent and moderately developed pulmonary arteries were supplied by a left ductus arteriosus (Fig. 2). In only one case (Fig. 3a), were we unable to identify either a blind or a potential pulmonary infundibulum as a separate entity from the sinus portion of the right ventricle. In this heart, no trace of the conal septum was found below the root of the great arteries. Nevertheless, a thin, fibrous, cordlike structure connected the heart with two confluent and relatively large pulmonary arteries into which a wide left ductus arteriosus opened. On histology, the fibrous cord was shown to be a vascular structure with a lumen and an elastic medial layer, and thus it was interpreted as a pulmonary trunk (Fig. 3b).

The anterior septal leaflet of the tricuspid valve was in fibrous continuity with the posterior aortic cusp in all but one case in which a small muscular band was interposed between these structures.

The left ventricular outflow tract always showed mitral-aortic fibrous continuity.

The ventricular septal defect was inferior and posterior to the deviated conal septum and derived from the aortic overriding and from the malalignment between the conal and ventricular septa, as described in specimens of tetralogy of Fallot (Becker *et al.*, 1975).

The membranous septum was partially formed, constituting the posterior rim of the ventricular septal defect in all but one case. In two instances, this partially formed interventricular component was sufficiently redundant to produce some occlusion of the right ventricular outflow to the aorta (Fig. 4).

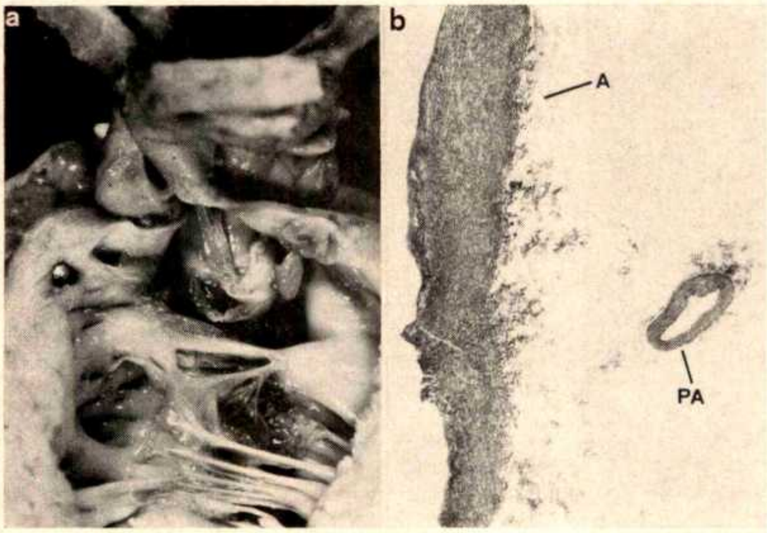

Fig. 3 *Morphology of the right ventricular outflow tract in pulmonary atresia with ventricular septal defect and no macroscopically recognisable pulmonary trunk or infundibulum. (a) The right ventricular outflow tract is similar to that described in truncus arteriosus communis without remnants of the conal septum. (b) Histology of the root of the aorta (A) shows a small vascular structure, with a lumen and an elastic medial layer, which represents the main pulmonary artery (PA). (Elastic van Gieson stain. ×12.)*

(b) *Arterioventricular alignment and aortic arch*
The aorta arose from the right ventricle to an extent which varied between 50 and 100 per cent. There was no relation between the degree of aortic overriding and the underdevelopment of the pulmonary infundibulum. The aortic arch was left-sided in 13 cases and right-sided in 5; 4 of the latter had a left ductus arteriosus.

(c) *Coronary arterial patterns*
The aortic root, as viewed from the ventricular aspect, was rotated clockwise so that the right coronary cusp was displaced anteriorly. In all instances the coronary arteries arose from the 2 sinuses adjacent to the atretic infundibulum. In 2 cases the epicardial course of the coronary arteries was abnormal in that the anterior descending branch arose from the right coronary artery and crossed the right ventricular infundibulum to reach the septum.

(d) *Systemic-pulmonary arterial supply, size of pulmonary trunk, and of its main branches*
The right and left pulmonary arteries were always confluent. In 7 specimens a ductus arteriosus was persistent, the pulmonary trunk was hypoplastic or rudimentary (absent in one case) and the pulmonary arteries, though well developed, were

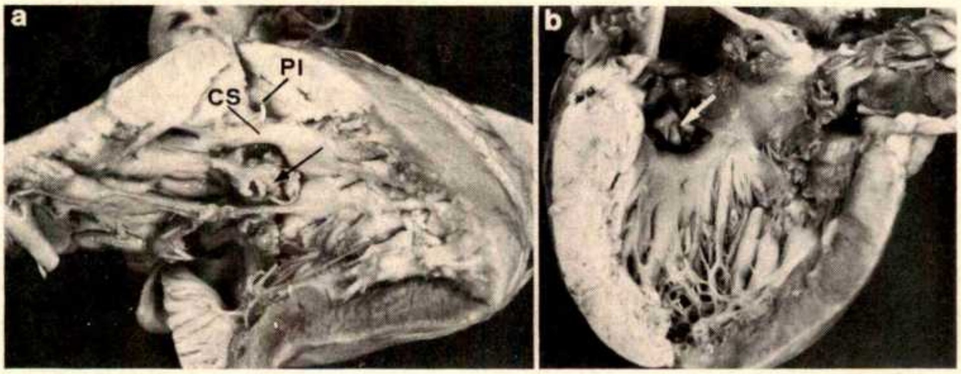

Fig. 4 *Fibrous tissue (arrows) from membranous septum and septal leaflet of the tricuspid valve is so redundant that the aortic outflow tract from the right ventricle is obstructed. CS, conal septum; PI, pulmonary infundibulum. (a) Right ventricular view; (b) left ventricular view.*

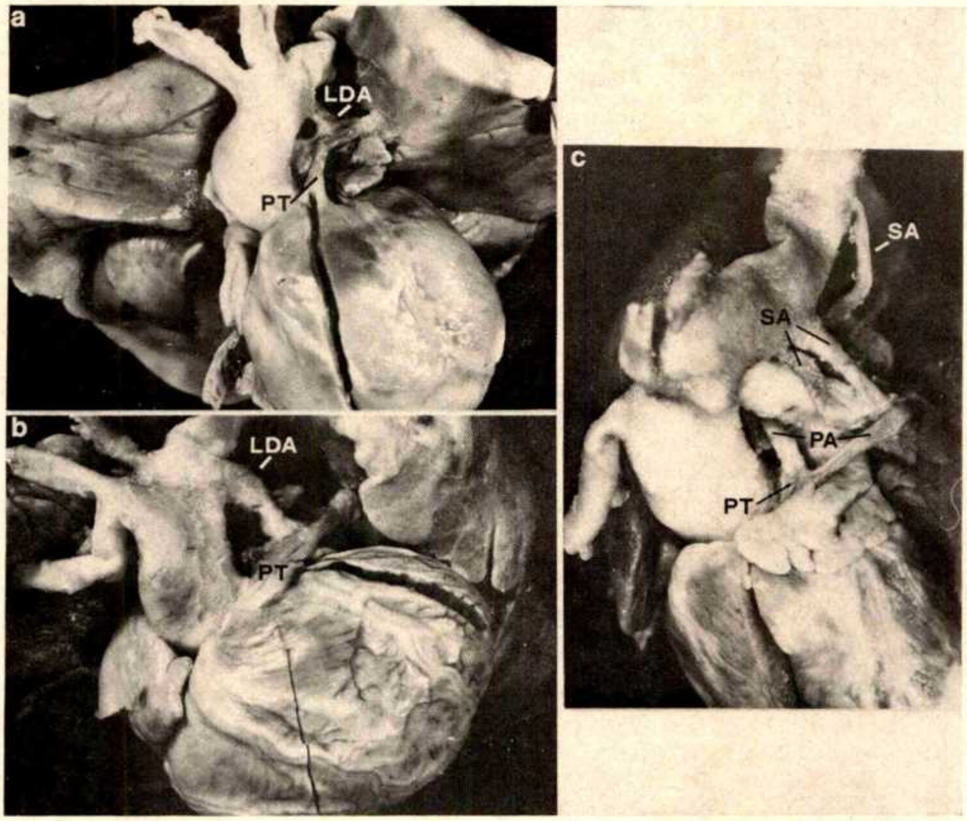

Fig. 5 *Pulmonary arterial supply in 3 examples of pulmonary atresia with ventricular septal defect and normally related great arteries. (a) A left sided ductus arteriosus (LDA) connects a left aortic isthmus with the left pulmonary artery. The pulmonary trunk (PT) is hypoplastic and the pulmonary arteries smaller than normal. (b) A large left ductus arteriosus (LDA) is the only source of pulmonary arterial supply as in case (a). Here the pulmonary trunk and arteries are normal in size. (c) Agenesis of the ductus arteriosus. The pulmonary arterial supply is furnished by 3 systemic pulmonary arteries (SA), 2 for the left lung and 1 for the right lung: the 3 vessels do not connect with the major pulmonary arteries (PA). The pulmonary trunk and arteries are extremely hypoplastic.*

smaller than normal. No systemic-pulmonary anastomotic vessels were observed in these cases (Fig. 5a).

Three specimens showed a good sized pulmonary trunk and pulmonary arteries with a wide ductus arteriosus and no other systemic-pulmonary arterial supply (Fig. 5b).

In 7 other specimens the ductus was absent and the pulmonary trunk and its main branches were severely hypoplastic. Small systemic-pulmonary arteries, originating from the descending aorta, entered both lungs without anastomosing with the major pulmonary arteries at the hilum (Fig. 5c).

Finally, in one case, even though the ductus was absent, the pulmonary trunk and the pulmonary arteries were of reasonable size, because of the existence of a direct anastomosis at the hilum of the right lung, between the right pulmonary artery and a large systemic-pulmonary artery arising from the descending aorta (Fig. 6). In the same patient other large systemic-pulmonary arteries entered both lungs without anastomosing with the proximal pulmonary vascular bed (Fig. 6b). This patient, who died of left ventricular failure at age 9 months without undergoing operation, was acyanotic. Histological examination of his lungs disclosed mild medial hypertrophy of the small pulmonary arteries and arterioles (Fig. 6d).

GROUP 2: PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT AND POSTERIORLY SITUATED PULMONARY TRUNK (7 CASES)

The morphological features of this group may be summarised as follows (Fig. 7).

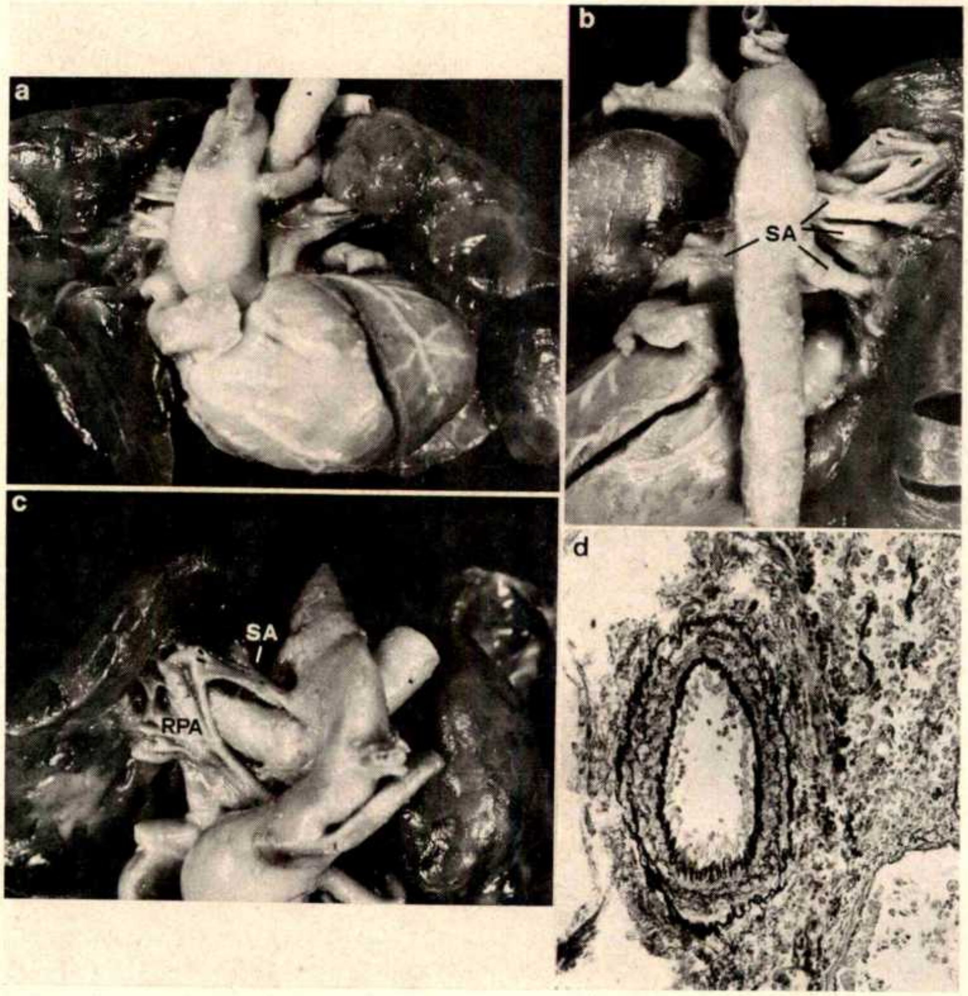

Fig. 6 *Pulmonary arterial supply in a case of pulmonary atresia with ventricular septal defect and normally related great arteries in which the ductus was absent. (a) Anterior external view: though the ductus arteriosus is absent the pulmonary trunk and arteries are normally sized. (b) Posterior view (oesophagus and trachea removed): four large systemic-pulmonary arteries (SA) arise from the descending aorta, one for the left lung and three for the right lung. (c) One of these large systemic arteries (SA) anastomoses with the right pulmonary artery (RPA) at the hilum of the right lung. (d) Histology of the lungs reveals mild medial hypertrophy and duplication of the elastic layers in the small muscular pulmonary arteries. (Elastic van Gieson stain. ×150.)*

(a) The aortic root arose entirely from the right ventricle without overriding the left (Fig. 7a), except in one case when there was 50 per cent override (Fig. 7b).

(b) The subaortic conus showed a muscular band (conoventricular flange) interposed between the aortic and the atrioventricular valves.

(c) The ventricular septal defect derived from a partial or complete absence of conal septum and was situated below it.

(d) In all hearts the pulmonary circulation was supported only by a ductus arteriosus with moderately-sized pulmonary arteries, while systemic-pulmonary anastomotic vessels were never seen.

Discussion

PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT AND NORMALLY RELATED GREAT ARTERIES

The present findings and our previous observations (Thiene *et al.*, 1976) constitute strong evidence that

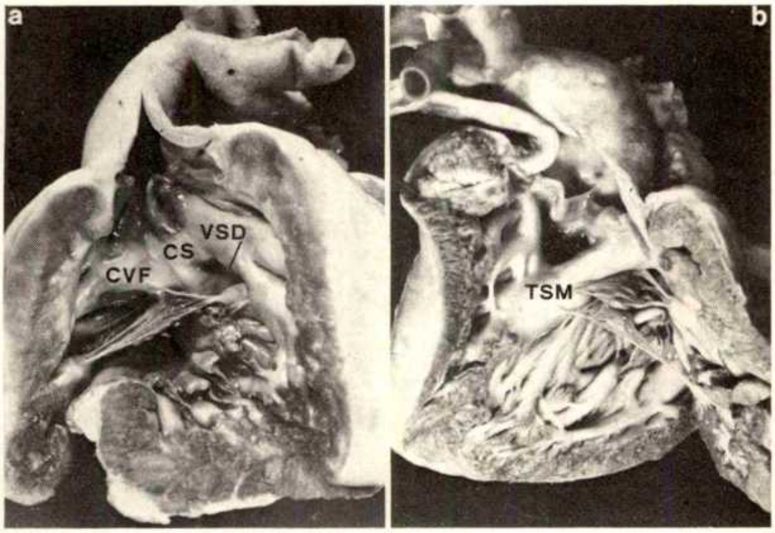

Fig. 7 *Right ventricular outflow tract morphology and types of ventricular septal defect in pulmonary atresia with ventricular septal defect and posterior atretic pulmonary artery.* *(a) The aorta arises entirely from the right ventricle above a muscular conus. The ventricular septal defect (VSD) is an intracristal defect and the conal and ventricular septa are normally aligned (from a patient with situs inversus, laevocardia and atrioventricular discordance). CS, conal septum; CVF, conoventricular flange.* *(b) The aorta presents with biventricular origin and the ventricular septal defect, which lies between the anterior and posterior limbs of the trabecula septomarginalis (TSM), derives from the absence of the conal septum (from a patient with situs inversus, dextrocardia, and atrioventricular concordance).*

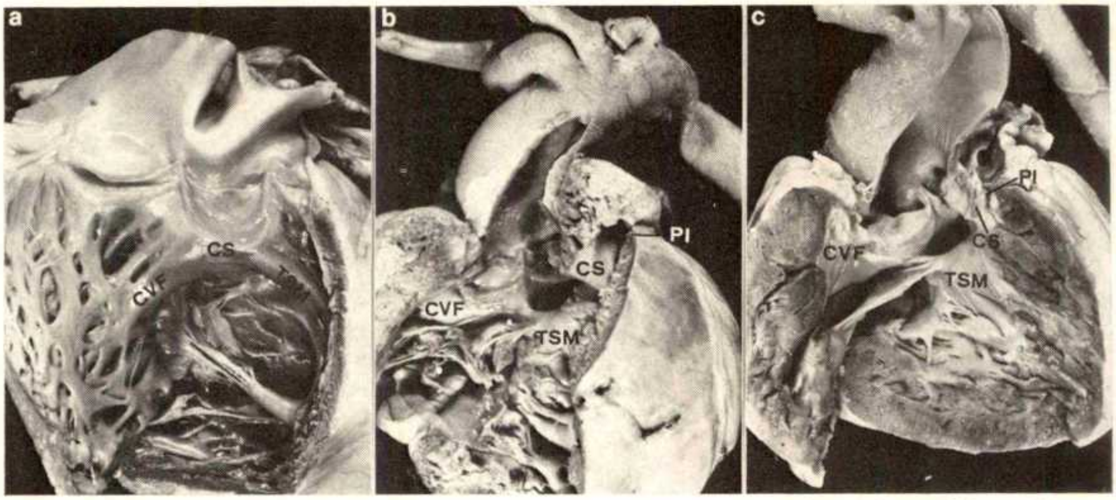

Fig. 8 *The spectrum of pulmonary outflow obstruction in normally related great arteries—(a) normal heart, (b) tetralogy of Fallot, (c) pulmonary atresia with ventricular septal defect. Note the progressive anterior deviation of the conal septum with its septal insertion in front of the trabecula septomarginalis. CS, conal septum; CVF, conoventricular flange; PI, pulmonary infundibulum; TSM, trabecula septomarginalis.*

the malformation of pulmonary atresia with ventricular septal defect and persistent truncus arteriosus is quite distinct, both morphologically and morphogenetically. In truncus arteriosus the septation of the cardiac outflow tracts is absent, thus resulting in a conal ventricular septal defect and a common semilunar valve. In contrast, in pulmonary atresia with ventricular septal defect unequal septation occurs at the expense of the pulmonary infundibulum, and the ventricular septal defect results from the aortic overriding and from the extreme malalignment between the anteriorly deviated conal septum and the interventricular septum (Goor *et al.*, 1971; Becker *et al.*, 1975). We, therefore, believe that it is confusing and misleading to group under the term 'absence of anatomic origin from the heart of pulmonary arterial supply' such dissimilar cardiac malformations as truncus arteriosus and pulmonary atresia even though both are characterised by discontinuity between the right ventricle and the pulmonary artery (McGoon *et al.*, 1970; Edwards and McGoon, 1973; Berry *et al.*, 1974). We also believe that our evidence militates against the concept proposed by Van Praagh that truncus arteriosus should be considered as extreme pulmonary atresia with ventricular septal defect and an aortopulmonary septal defect (Van Praagh and Van Praagh, 1965; Calder *et al.*, 1976; Van Praagh, 1976). Thus, in all our cases of pulmonary atresia with ventricular septal defect, derivatives of the sixth aortic arches were observed in the pericardial cavity and in all but one a pulmonary trunk arose from the heart base suggesting truncal septation. In the single specimen in which a main pulmonary artery could not be identified, even by histology, the intracardiac anatomy of the right ventricle showed an atretic pulmonary infundibulum with a distinct conal septum remnant. Thus in all our specimens signs of conal, truncal, or truncoconal septation were present. These findings indicate that pulmonary atresia should be included in the spectrum of tetralogy of Fallot as it is characterised by the same, albeit extreme, malseptation, i.e. conal rotation and anterior deviation of the conus septum which determine, respectively, dextroposition of the aorta and atresia of the pulmonary infundibulum (Fig. 8). Furthermore, pathological evidence shows that pulmonary atresia with ventricular septal defect and absent ductus arteriosus participates in the spectrum of Fallot's tetralogy in Keeshond dogs with hereditary defects of the conotruncal septum (Patterson *et al.*, 1974). In contrast, much of the evidence at present available shows that persistent truncus arteriosus results from failure of septation of the embryonic infundibula and truncus (Thiene *et al.*, 1976; Crupi *et al.*, 1977).

PULMONARY CIRCULATION IN PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT AND NORMALLY RELATED GREAT ARTERIES

In pulmonary atresia with ventricular septal defect, unlike truncus arteriosus, the pulmonary circulation does not originate directly from the ascending aorta. The alternative sources of pulmonary blood supply are either the ductus arteriosus or systemic-pulmonary anastomotic vessels which arise from the descending aorta.

In 38 per cent of our cases the ductus arteriosus was absent, thus determining extreme underdevelopment of the pulmonary arteries. Under these conditions the pulmonary arterial supply is furnished only by systemic vessels which anastomose intraparenchymally with the intrapulmonary arterial bed. In a single specimen presenting with absent ductus, the pulmonary trunk and its branches were wide because of a proximal anastomosis at the hilum between the right pulmonary artery and a large systemic vessel. On the other hand, in the 10 cases where a ductus arteriosus was present, the pulmonary arteries had a diameter ranging from half normal to normal size. Our findings are in agreement with those of Bharati *et al.* (1975) regarding the inverse relation between the presence of a ductus arteriosus and the presence of systemic–pulmonary arteries. Angiographic investigations have also shown that systemic-pulmonary arteries and ductus arteriosus do not coexist (Macartney *et al.*, 1974).

According to Jefferson *et al.* (1972), there are two basically different types of collateral vessels, namely large and small. Macartney *et al.* (1974) argued that the small type might be acquired, but our findings of small systemic-pulmonary anastomotic vessels in specimens from newborn patients lead us to disagree with this deduction.

Various terms have been suggested to describe these anastomotic vessels: bronchial arteries (Chesler *et al.*, 1974), aortico-pulmonary collateral arteries (Kouchoukos *et al.*, 1971; Macartney *et al.*, 1974), and systemic arteries (Jefferson *et al.*, 1972). The term 'bronchial arteries' is inaccurate from both an anatomical and embryogenetic point of view. The arteries may take origin from brachiocephalic arteries or subdiaphragmatic aorta as well as from the thoracic aorta (McGoon *et al.*, 1975). Moreover, these arteries derive from the primitive intersegmental branches of the dorsal aortae which supply the lung bud early in embryonic life (Congdon, 1922; Boyden, 1970), and we believe that these arteries should be called systemic-pulmonary arteries. The persistence of these early embryological connections between the systemic and pulmonary circulations occurs in pulmonary atresia whenever the distal sixth aortic arch (ductus arteriosus) fails to develop. Furthermore, this failure may occur in other situations. Thus absence of septation of the cardiac outflow tracts in truncus arteriosus may render superfluous the growth of the sixth aortic arches as a second connection between the ventral and dorsal aortae, thus determining the persistence of intersegmental arteries as the only source of pulmonary blood supply, such as seen in persistent truncus arteriosus with absent pulmonary arteries ('type IV') (Table).

PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT VERSUS TRUNCUS ARTERIOSUS TYPE IV

Taussig *et al.* (1973) have suggested that 'pseudo' truncus arteriosus is not a variant of tetralogy of Fallot and that a 'pseudo' truncus arteriosus and a truncus arteriosus type IV are basically the same malformation even though in the former a rudimentary pulmonary artery can be shown at necropsy either through gross or microscopial examination. In similar fashion, Stuckey *et al.* (1968) applied the name 'absent sixth aortic arch' to cases in which derivatives of the sixth aortic arches were present though completely atretic.

It seems to us that these statements add further confusion to an already confused topic. In our opinion it is vital to distinguish between agenesis and atresia of an artery. Thus, the finding of a fibrous strand connecting the heart base to the lungs is incompatible with absence or agenesis of the sixth aortic arches. The fundamental question must, therefore, be as to whether or not the sixth arches have developed. In truncus arteriosus with absent pulmonary arteries ('type IV'), they have not developed, since no remnants of pulmonary arteries are observed (Thiene *et al.*, 1976). In contrast, in pulmonary atresia with ventricular septal defect, at the very least a fibrous cordlike remnant of the sixth arch is seen within the pericardial cavity, as described in this study. Clearly, at times this distinction may be difficult if not impossible to reach by means of clinical investigation (Jefferson *et al.*, 1972; Macartney *et al.*, 1973; Chesler *et al.*, 1974). None the less, we believe that the distinction should be maintained, since the two malformations are developmentally and morphologically distinct.

Table

Defect	*Embryology*
Truncus arteriosus communis	Absent truncoconal septation with or without distal 6th aortic arch
Persistent truncus arteriosus type IV	Absent truncoconal septation + agenesis 6th aortic arches + persistence of early systemic-pulmonary connections
Pulmonary atresia with ventricular septal defect and without ductus arteriosus	Extreme unequal truncoconal septation + agenesis of distal 6th aortic arches + persistence of early systemic-pulmonary connections
Pulmonary atresia with ventricular septal defect and with ductus arteriosus	Extreme unequal truncoconal septation with normal development of 6th aortic arches

Other authors (Somerville, 1970; Macartney *et al.*, 1974) have considered truncus arteriosus 'type IV' as an extreme form of atresia of the pulmonary infundibulum associated with agenesis of the pulmonary arteries. While cases of pulmonary atresia without a pulmonary infundibulum have been reported (Allanby *et al.*, 1950; Chesler *et al.*, 1974), no specimen of complete agenesis of the main pulmonary trunk and pulmonary arteries which exhibits a blind or potential pulmonary infundibulum has thus far been described. It could be argued that truncus arteriosus 'type IV' should not be regarded as truncus arteriosus 'communis' since the absent pulmonary arteries are not contributing to the single arterial trunk. However, if the term 'persistent' instead of 'communis' is used to indicate the truncus arteriosus, as at present, then the anomaly of truncus arteriosus 'type IV' can correctly be termed persistent truncus arteriosus with absent pulmonary arteries, since the anomaly, in addition to exhibiting agenesis of the sixth aortic arches, also possesses a single undivided conotruncus (Thiene *et al.*, 1976).

DIAGNOSTIC AND SURGICAL CONSIDERATIONS

It is difficult to distinguish angiocardiographically between persistent truncus with absent pulmonary arteries and pulmonary atresia with ventricular septal defect when no blind pulmonary infundibulum can be seen and the ductus arteriosus or proximal connections between systemic pulmonary vessels and pulmonary arteries are absent (Jefferson *et al.*, 1972; Chesler *et al.*, 1974; Macartney *et al.*, 1974). The distribution pattern of the systemic-pulmonary arteries is often similar in both conditions; therefore, only direct morphological or surgical observation may establish the presence or absence of sixth aortic arch derivatives, though some authors have argued that it may be expedient to ignore these differences (Crupi *et al.*, 1977).

It is significant that the angiocardiographic features of pulmonary atresia with obstructed ventricular septal defect, secondary to the presence of redundant tissue of the membranous septum, may resemble those of pulmonary atresia with intact ventricular septum and reversed intra-atrial shunt (Scott *et al.*, 1976). It is vital that the two be distinguished, since the prognosis of the two anomalies differs considerably.

Radical surgical correction of pulmonary atresia with ventricular septal defect may be considered only if the right and left pulmonary arteries are well developed (Berry *et al.*, 1974). On this basis, in 7 of our 18 hearts (39%) the pulmonary arteries were too hypoplastic to be used even for palliative surgery.

The systemic-pulmonary arteries theoretically could be used to reconstruct the continuity between the heart and the pulmonary arterial bed. However, their small size and their multiplicity, together with their frequent intrahilar stenoses (Macartney *et al.*, 1973; Chesler *et al.*, 1974) and extrapericardial location make them, for the most part, unsuitable for surgery.

Should it be possible to perform reconstructive surgery, then all of the systemic-pulmonary vessels must be ligated in order to prevent a persistent left-to-right shunt postoperatively (McGoon *et al.*, 1975). Pulmonary overperfusion may be a feature of the disease whenever large and multiple systemic-pulmonary arteries anastomose proximally with the pulmonary arteries (Stuckey *et al.*, 1968; Danilowicz and Ross, 1971).

The finding of specimens where the anterior descending coronary artery, arising from the right coronary artery, crossed the right ventricular infundibulum, confirms previous observations on coronary arterial patterns in pulmonary atresia (Bharati *et al.*, 1975) and Fallot's tetralogy (Fellows *et al.*, 1975). This anomaly can represent an additional surgical difficulty but it might be possible to determine this preoperatively by coronary arteriography.

PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT AND POSTERIOR ATRETIC PULMONARY ARTERY

The condition is characterised by discontinuity between the left ventricle and the pulmonary arterial bed. Surgical repair has been performed also in this variety of pulmonary atresia with ventricular septal defect (Marcelletti *et al.*, 1976).

In all our specimens the source of the pulmonary blood supply was the ductus arteriosus, and systemic-pulmonary arteries were not seen. Moreover, the ventricular septal defect was never a conal malalignment defect, as is the case in pulmonary atresia with normally related great arteries, because the aorta rarely presents with biventricular origin. A ventricular septal defect without malalignment has been previously described in this type of pulmonary atresia (Kugel, 1931; Young and Griswold, 1951; Kelsey *et al.*, 1953) but its morphogenetic significance has never been underlined. In fact, the mechanism determining atresia of the pulmonary outflow tract in this condition does not seem to depend on the deviation of the conal septum as much as it does in the form with normally related great arteries.

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References

Allanby, K. D., Brinton, W. D., Campbell, M., and Gardner, F. (1950). Pulmonary atresia and the collateral circulation to the lungs. *Guy's Hospital Reports*, **99**, 110–152.

Becker, A. E., Connor, M., and Anderson, R. H. (1975). Tetralogy of Fallot: a morphometric and geometric study. *American Journal of Cardiology*, **35**, 402–412.

Berry, B. E., McGoon, D. C., Ritter, D. G., and Davis, G. D. (1974). Absence of anatomic origin from heart of pulmonary arterial supply. Clinical application of classification. *Journal of Thoracic and Cardiovascular Surgery*, **68**, 119–125.

Bharati, S., Paul, M. H., Idriss, F. S., Potkin, R. T., and Lev, M. (1975). The surgical anatomy of pulmonary atresia with ventricular septal defect: pseudotruncus. *Journal of Thoracic and Cardiovascular Surgery*, **69**, 713–721.

Boyden, E. A. (1970). The time lag in the development of bronchial arteries. *Anatomical Record*, **166**, 611–614.

Calder, L., Van Praagh, R., Van Praagh, S., Sears, W. P., Corwin, R., Levy, A., Keith, J. D., and Paul, M. H. (1976). Truncus arteriosus communis. Clinical angiocardiographic and pathologic findings in 100 patients. *American Heart Journal*, **92**, 23–38.

Chesler, E., Beck, W., and Schrire, V. (1970). Selective catheterization of pulmonary or bronchial arteries in the preoperative assessment of pseudotruncus arteriosus and truncus arteriosus type IV. *American Journal of Cardiology*, **26**, 20–24.

Chesler, E., Matisonn, R., and Beck, W. (1974). The assessment of the arterial supply to the lungs in pseudotruncus arteriosus and truncus arteriosus type IV in relation to surgical repair. *American Heart Journal*, **88**, 542–552.

Congdon, E. D. (1922). Transposition of the aortic arch system during the development of the human embryo. *Contributions to Embryology (Carnegie Institute)*, **14**, Nos. 65–71, 47–110.

Crupi, G., Macartney, F. J., and Anderson, R. H. (1977). Persistent truncus arteriosus. A study of autopsied material with special reference to its definition and morphogenesis. *American Journal of Cardiology*, in press.

Danilowicz, D., and Ross, J., Jr. (1971). Pulmonary atresia without cyanosis. Report of two cases with ventricular septal defect and increased pulmonary blood flow. *British Heart Journal*, **33**, 138–141.

Doty, D. B., Kouchoukos, N. T., Kirklin, J. W., Barcia, A., and Bargeron, L. M. (1972). Surgery for pseudotruncus arteriosus with pulmonary blood flow originating from upper descending thoracic aorta. *Circulation*, **45-46**, Suppl. I, 121–129.

Edwards, J. E., Carey, L. S., Neufeld, H. N., and Lester, R. G. (1965). *Congenital Heart Disease*, W. B. Saunders, Philadelphia and London.

Edwards, J. E., and McGoon, D. C. (1973). Absence of anatomic origin from heart of pulmonary arterial supply. *Circulation,* **47,** 393–398.

Fellows, K. E., Freed, M. D., Keane, J. F., Van Praagh, R., Bernhard, W. F., and Castaneda, A. C. (1975). Results of routine preoperative coronary angiography in tetralogy of Fallot. *Circulation,* **51,** 561–566.

Goor, D. A., Lillehei, C. W., and Edwards, J. E. (1971). Ventricular septal defects and pulmonic stenosis with and without dextroposition. Anatomic features and embryologic implications. *Chest,* **60,** 117–128.

Jefferson, K., Rees, S., and Somerville, J. (1972). Systemic arterial supply to the lungs in pulmonary atresia and its relation to pulmonary artery development. *British Heart Journal,* **34,** 418–427.

Kelsey, J. R., Gilmore, C. E., and Edwards, J. E. (1953). Bilateral ductus arteriosus representing persistence of each sixth aortic arch. Report of a case in which there were associated isolated dextrocardia and ventricular septal defects. *Archives of Pathology,* **55,** 154–161.

Kouchoukos, N. T., Barcia, A., Bargeron, L. M., and Kirklin, J. W. (1971). Surgical treatment of congenital pulmonary atresia with ventricular septal defect. *Journal of Thoracic and Cardiovascular Surgery,* **61,** 70–84.

Kugel, M. A. (1931). A clinical and pathological study of two cases of truncus solitarius aorticus (pulmonary atresia). *American Heart Journal,* **7,** 262–273.

McGoon, D. C., Baird, D. K., and Davis, G. D. (1975). Surgical management of large bronchial collateral arteries with pulmonary stenosis or atresia. *Circulation,* **52,** 109–118.

McGoon, D. C., Rastelli, G. C., and Wallace, R. B. (1970). Discontinuity between right ventricle and pulmonary artery: surgical treatment. *Annals of Surgery,* **172,** 680–688.

Macartney, F. J., Deverall, P., and Scott, O. (1973). Haemodynamic characteristics of systemic arterial blood supply to the lungs. *British Heart Journal,* **35,** 28–37.

Macartney, F. J., Scott, O., and Deverall, P. B. (1974). Haemodynamic and anatomical characteristics of pulmonary blood supply in pulmonary atresia with ventricular septal defect—including a case of persistent fifth aortic arch. *British Heart Journal,* **36,** 1049–1060.

Marcelletti, C., Mair, D. D., McGoon, D. C., Wallace, R. B., and Danielson, G. K. (1976). Complete repair of transposition of the great arteries with pulmonary atresia. *Journal of Thoracic and Cardiovascular Surgery,* **72,** 215–220.

Miller, W. W., Nadas, A. S., Bernhard, W. F., and Gross, R. E. (1968). Congenital pulmonary atresia with ventricular septal defect. Review of the clinical course of fifty patients with assessment of the results of palliative surgery. *American Journal of Cardiology,* **21,** 673–680.

Munoz-Armas, S., Anselmi, G., de la Cruz, M., and Machado, I. (1964). Pulmonary atresia with biventricular aorta. *British Heart Journal,* **26,** 606–613.

Pacifico, A. D., Kirklin, J. W., Bargeron, L. M., and Soto, B. (1974). Surgical treatment of common arterial trunk with pseudotruncus arteriosus. *Circulation,* **49-50,** Suppl. II, 20–25.

Patterson, D. F., Pyle, R. L., Van Mierop, L., Melbin, J., and Olson, M. (1974). Hereditary defects of the conotruncal septum in Keeshond dogs: pathologic and genetic studies. *American Journal of Cardiology,* **34,** 187–205.

Ross, D. N., and Somerville, J. (1966). Correction of pulmonary atresia with a homograft aortic valve. *Lancet,* **2,** 1446–1449.

Scott, O., Macartney, F. J., and Deverall, P. B. (1976). Anomalous accessory tricuspid valve tissue causing reduction in the size of ventricular septal defect (abstract). *European Journal of Cardiology,* **4,** 259.

Shinebourne, E. A., Macartney, F. J., and Anderson, R. H. (1976). Sequential chamber localization—logical approach to diagnosis in congenital heart disease. *British Heart Journal,* **38,** 327–340.

Somerville, J. (1970). Management of pulmonary atresia. *British Heart Journal,* **32,** 641–651.

Somerville, J., and Ross, D. (1972). Long term results of complete correction with homograft reconstruction in pulmonary outflow tract atresia. *British Heart Journal,* **34,** 29–36.

Stuckey, D., Bowdler, J. D., and Reye, R. D. K. (1968). Absent sixth aortic arch: a form of pulmonary atresia. *British Heart Journal,* **30,** 258–264.

Taussig, H. B., Momberger, N., and Kink, H. (1973). Long time observations on the Blalock-Taussig operation. VI: Truncus arteriosus type IV. *Johns Hopkins Medical Journal,* **133,** 123–147.

Thiene, G., Bortolotti, U., Gallucci, V., Terribile, V., and Pellegrino, P. A. (1976). Anatomical study of truncus arteriosus communis with embryological and surgical considerations. *British Heart Journal,* **38,** 1109–1123.

Van Praagh, R. (1976). Classification of truncus arteriosus communis (TAC). *American Heart Journal,* **92,** 129–132.

Van Praagh, R., and Van Praagh, S. (1965). The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. A study of 57 necropsy cases. *American Journal of Cardiology,* **16,** 406–425.

Young, M. D., and Griswold, H. E. (1951). Situs inversus of the abdominal viscera with levocardia. Report of eight cases submitted to the Blalock-Taussig operation. *Circulation,* **3,** 202–214.

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Coronary arteries in d-transposition

A necropsy study of reimplantation

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The coronary arteries are a major concern in anatomical correction of d-transposition of the great arteries. This necropsy study was undertaken to assess the feasibility of direct bilateral reimplantation as described by Jatene et al. *This seemed possible in only 30 per cent of 100 cases, and furthermore was related to the type of coronary artery pattern.*

Direct anatomical correction of d-transposition of the great arteries has stimulated increasing interest since the first favourable surgical results were reported (Jatene *et al.*, 1976). However, initial enthusiasm has been tempered by several failures. Poor results have been explained by high pulmonary vascular resistance in cases with an open septum (Jatene *et al.*, 1976) and by poor left ventricular function in cases with an intact ventricular septum (Major *et al.*, 1976). There are also technical problems related to how and where to cut the aorta and the pulmonary arteries to avoid tension and compression, and to the reimplantation of the coronary arteries.

Balderman *et al.* (1974) studied the anatomical mobility of the coronary arteries in 58 hearts with transposition of the great arteries. Coronary artery pattern in all their specimens belonged to type 1 of the Shaher and Puddu classification (Shaher and Puddu, 1966). The authors found that both coronary arteries were movable in 48 per cent of the cases, and concluded that coronary artery anatomy in transposition of the great arteries was such that direct switching of the vessels to achieve anatomical correction was possible.

To investigate this problem further, coronary artery anatomy was studied in 100 necropsy cases of transposition of the great arteries under 4 months of age, belonging to most types of the Shaher classification. Satisfactory direct reimplantation of both coronary arteries as described by Jatene *et al.* (1976) seemed possible in only 30 per cent of the cases.

Material and methods

The study comprised 100 formalin preserved hearts of infants with transposition of the great arteries, dying under 4 months of age; poorly preserved or damaged specimens were excluded.[1]

Drawings of the initial portion of the coronary arteries were made, to study the disposition of the first branches. Measurements were then made from the ostium to the first branch of each artery. Finally, the origins of the coronary arteries were dissected and the ostia excised with a ring of adjacent aortic wall and brought to the nearest suitable reimplantation site on the pulmonary artery. Excessive traction or kinking was avoided either by division of the first branch, or by interposition of a graft.

Results

Coronary artery patterns could be classified as follows (Fig. 1).

Group 1: 65 cases. The left coronary artery arises from a single ostium above the left sinus and divides into the anterior descending and the left circumflex arteries. The right coronary artery arises from a single ostium above the posterior sinus and divides into descending and marginal arteries.

Group 2: 22 cases. The left sinus gives rise to the left anterior descending artery alone. The left circumflex and right coronary arteries arise from the posterior sinus.

Group 3: 6 cases. The posterior sinus gives rise to all 3 major arteries. In 4 of the cases, there was also a vessel arising from a small ostium above the left sinus, with branches to the interventricular septum and the adjacent anterior wall of the left and right ventricles.

Group 4: 3 cases. The left sinus gives rise to all 3 major arteries. In all 3 cases there was also a

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[1] All specimens were studied at the Department of Pediatric Cardiology, Pr Ribiere, Hopital Parrot-Bicetre, Paris, France.

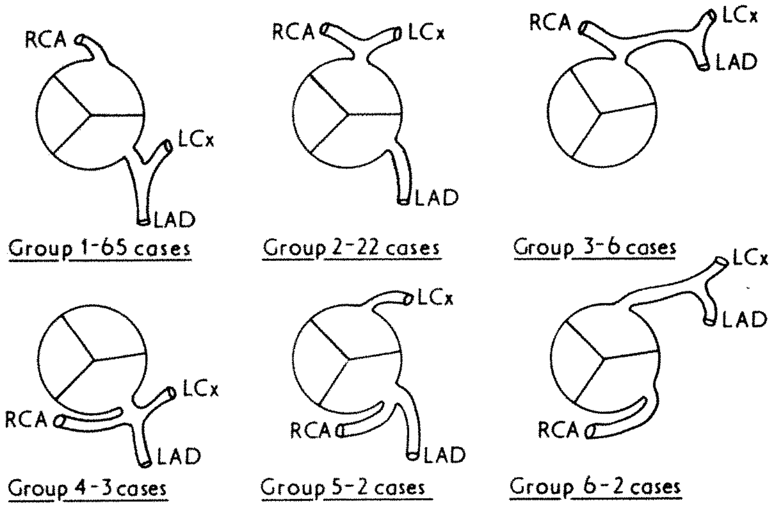

Fig. 1 *Coronary arteries in 100 cases of d-transposition of the great arteries. LAD, left anterior descending artery; LCx, left circumflex; RCA, right coronary artery.*

vessel arising from tiny posterior ostium, with small branches to the left and right atria and interatrial septum.

Group 5: 2 cases. The left sinus gives rise to the left anterior descending and right coronary arteries. The left circumflex artery alone arises from a posterior ostium.

Group 6: 2 cases. The left sinus gives rise to the right coronary artery. The posterior sinus gives rise to a long left coronary artery which divides into anterior descending and left circumflex arteries on the left side of the pulmonary artery.

REIMPLANTATION IN GROUP I

Reimplantation of left coronary artery

Direct reimplantation was possible in 36 of the 65 cases. In 15 cases it was necessary to ligate and divide the first branch artery to make it possible to reimplant the ostium. In 14 cases interposition of a graft was necessary. Several factors determined the feasibility of reimplantation.

(1) The length of the left main coronary artery before dividing into anterior descending and left circumflex arteries, (2) the distribution of the first branch arteries which arise before the division into anterior descending and left circumflex arteries, and (3) the exact position of the pulmonary artery.

In 18 cases the left main coronary artery had no branches before dividing into the anterior descending and left circumflex arteries, and varied from 1 to 8 mm in length (Table 1). In 47 cases the left coronary artery gave rise to branches directed towards the right before or at the point of division into anterior descending and left circumflex (Table 2); these tend to anchor the initial segment of the left coronary artery. They usually cause no difficulty if they are very oblique or arise close to the origin of anterior descending artery. They seriously interfere with direct reimplantation when they are perpendicular to the left coronary artery or close to the coronary ostium (Fig. 2).

The exact position of the pulmonary artery is

Table 1 *Group 1: Length of left main coronary artery in 18 cases with no branches before division into anterior descending and circumflex arteries.*

Length (mm)	*No. of cases*
1	1
2	1
3	7
4	3
5	3
6	2
8	1

Table 2 *Group 1: Length of left main coronary artery before first branch in 47 cases*

Length (mm)	*No. of cases*
0	5
0·5	6
1	5
2	13
3	8
4	5
5	3
6	1
7	1

also relevant. This may be relatively posterior or may be close to the origin of the left coronary artery, allowing even a short initial segment to be reimplanted.

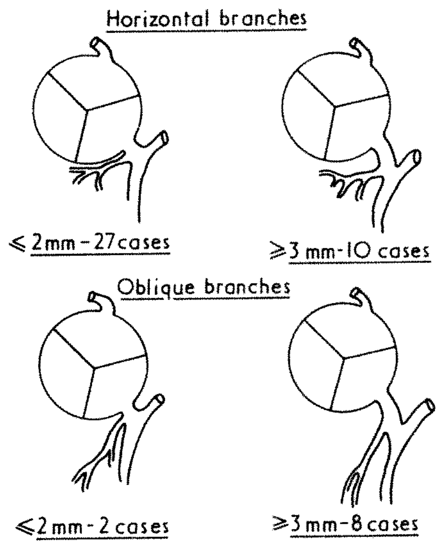

Fig. 2 *Left coronary artery in group 1. Regrouping of 47 cases, in whom first branch arose before division into circumflex and anterior descending arteries, according to orientation and distance from ostium of first branches.*

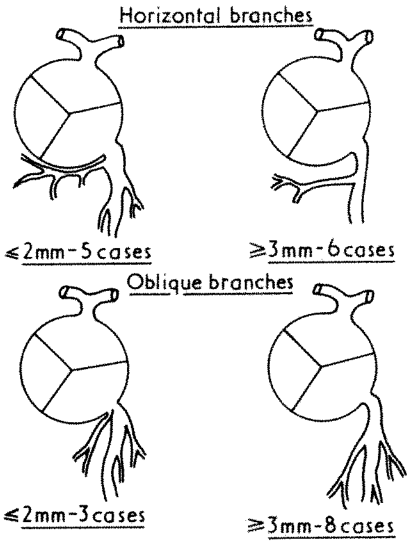

Fig. 3 *Left anterior descending coronary artery in group 2. Orientation and distance from ostium of first branches.*

Reimplantation of right coronary artery
The free initial segment before the first branch artery, either to the atrium or the right marginal artery, was between 0·5 and 10 mm in length (Table 3). Direct reimplantation was possible in 48 cases. When the first branch of the right coronary artery was to the right atrium (31 cases), direct reimplantation was possible in 20 cases, division of the first branch was necessary in 10, and interposition of a graft in 1. When the first branch was the marginal artery, direct reimplantation was possible in 28, but interposition of a graft was necessary in the other 6 cases.

REIMPLANTATION IN GROUP 2

Reimplantation of left anterior descending artery
Direct reimplantation was possible in 12 of the 22 cases. In 4 cases the first branch artery had to be divided. In 6 cases interposition of a graft was necessary. The possibility of direct reimplantation depends essentially on the position of first branches as described for group 1 (Table 4, Fig. 3).

Reimplantation of right coronary artery
In this group the right coronary artery divided into the posterior descending and left circumflex arteries. The division was immediate, with 2 adjacent

Table 3 *Group 1: Distance from ostium of right coronary artery to first branch*

Length (mm)	*No. of cases*
1	4
2	6
3	11
4	17
5	7
6	8
7	5
8	3
9	1
10	3

Table 4 *Group 2: Distance from ostium of left anterior descending artery to first branch*

Length (mm)	*No. of cases*
0	2
0·5	2
1	1
2	3
3	5
4	2
5	2
6	1
7	2
10	2

posterior ostia, in 6 hearts. The distance between the ostium and the division varied between 0 and 6 mm (Table 5). A small branch to the atrial wall and septum arose from the bifurcation into the posterior descending and left circumflex arteries in 8 cases.

Direct implantation seemed possible in only 1 case. Interposition of a graft was necessary in the other 21 cases. The obstacle to direct reimplantation is that when the ostium is detached and displaced towards the pulmonary artery on the left, the left circumflex artery is angulated and furthermore is compressed when the initial portion of the pulmonary artery is expanded. To avoid this, the artery should be dissected only from the ostium to the bifurcation, without mobilising the left circumflex or the posterior descending arteries, and a small graft placed between the detached ostium and the pulmonary artery 1 to 1·5 cm higher.

REIMPLANTATION IN GROUP 3

In this group all 3 major arteries arose from the posterior sinus. Interposition of a graft was necessary in all 6 cases for the same reasons as in the preceding group. In 4 cases there was also an ostium in the left sinus which could be reimplanted directly in 2, and needed a graft in 2.

Table 5 *Group 2: Distance from posterior ostium to division into left circumflex and right coronary arteries*

Length (mm)	*No. of cases*
0	6
0·5	4
1	3
2	3
3	2
4	1
5	1
6	1

REIMPLANTATION IN GROUP 4

In this group it was the left sinus that gave rise to the 3 major arteries. Displacing the ostium towards the pulmonary artery was limited by the right coronary artery and a graft was, therefore, necessary in all 3 cases. There was also a tiny posterior ostium in each case, for which there appeared to be no satisfactory solution.

REIMPLANTATION IN GROUP 5

In both cases, the ostium in the left sinus, from which the left anterior descending and right coronary arteries arose, could be directly reimplanted into the pulmonary artery. The posterior ostium giving rise to the left circumflex artery could also be reimplanted directly in both cases.

REIMPLANTATION IN GROUP 6

The ostium in the left sinus giving rise to the right coronary artery could be reimplanted directly in 1 case, but a graft was necessary in the other. The posterior ostium gave rise to the left coronary artery and divided into anterior descending and left circumflex arteries on the left side of the pulmonary artery; direct reimplantation was possible in both cases.

Discussion

This study was undertaken to evaluate the difficulties which would be encountered with coronary artery reimplantation during anatomical correction of transposition of the great arteries and to define particular problems related to the different coronary artery patterns. Reimplantation is not always easy and technical problems will certainly arise and be responsible for many failures.

In the 100 cases of transposition of the great

Table 6 *Reimplantation of coronary arteries in 100 cases of d-transposition*

Group	*No. of cases*	*Ostium*	*Arteries*	*Reimplantation*			
				Direct	*Division of early branch*	*Interposed graft*	*Impossible*
1	65	L sinus	LCA (LAD and LCx)	36	15	14	0
		Posterior sinus	RCA	48	10	7	0
2	22	L sinus	LAD	12	4	6	0
		Posterior sinus	RCA and LCx	1	0	21	0
3	6	Posterior sinus	LCA and RCA	0	0	6	0
		L sinus (4 cases only)	small branches	2	0	2	0
4	3	L sinus	LCA and RCA	0	0	3	0
		Posterior sinus	small branches	0	0	0	3
5	2	L sinus	LAD and RCA	2	0	0	0
		Posterior sinus	LCx	2	0	0	0
6	2	L sinus	RCA	1	0	1	0
		Posterior sinus	LCA	2	0	0	0
Total	100			106	29	60	3

arteries studied here, direct bilateral reimplantation was possible in only 30 cases: 26 were in group 1, 1 in group 2, 2 in group 5, and 1 in group 6. Bilateral grafts were necessary in 9 cases: 1 in group 1, 6 in group 2, and 2 in group 3. Direct reimplantation was possible in a total of 106 arteries; a graft was necessary for 60 arteries; and in 29 cases, the first branch had to be divided (Table 6).

The advisability of this procedure to lengthen the initial free segment seems questionable; if division of 'disturbing' branches is proscribed, a total of 89 grafts would be used, and bilateral grafting would become necessary in 7 cases in group 1 and 10 in group 2.

Additional problems with the coronary arteries may also arise after completion of the anatomical correction, as apparently satisfactory anastomoses may become twisted as a result of the dynamics of the beating working heart.

It is most probable that, because of the risks inherent in coronary artery reimplantation, the technique of aortopulmonary fenestration will be preferable (Planché, 1976).

References

Balderman, S. C., Athanasuleas, C. L., and Anagnostopoulos, C. E. (1974). Coronary artery anatomy in transposition of the great vessels in relation to anatomic surgical correction. *Journal of Thoracic and Cardiovascular Surgery*, **67**, 208–212.

Jatene, A. D., Fontes, V. F., Paulista, P. P., Souza, L. C. B., Neger, F., Galantier, M., and Sousa, J. E. M. R. (1976). Anatomic correction of transposition of the great vessels. *Journal of Thoracic and Cardiovascular Surgery*, **72**, 364–369.

Major, W. K., Matsuda, H., and Subramanian, S. (1976). Failure of the Jatene procedure in a patient with d-transposition and intact ventricular septum. *Annals of Thoracic Surgery*, **22**, 386–388.

Planché, C. (1976). La transposition des gros vaisseaux. *Nouvelle Presse Médicale*, **5**, 1991–1992.

Shaher, R. M., and Puddu, G. C. (1966). Coronary arterial anatomy in complete transposition of the great vessels. *American Journal of Cardiology*, **17**, 355–361.

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Left ventricular performance in patients with left ventricular hypertrophy caused by systemic arterial hypertension[1]

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To assess the adaptation of the left ventricle to a chronic pressure overload we used echocardiography to study 18 patients with left ventricular hypertrophy caused by systemic arterial hypertension. Increased values for either posterior wall or interventricular septal thickness or both confirmed the presence of left ventricular hypertrophy in all patients and an increase in the average wall thickness to radius ratio was consistent with the development of concentric hypertrophy. No patient had clinical evidence of ischaemic heart disease. Ejection phase indices of left ventricular performance (mean Vcf, fractional per cent of shortening, normalised posterior wall velocity, and ejection fraction) were within the normal range in the basal state in 16 of the 18 patients. The hypothesis is advanced that patients with concentric left ventricular hypertrophy resulting from systemic arterial hypertension usually have normal left ventricular performance in the basal state because values for wall stress remain within the normal range. We conclude that the hypertrophic response to a chronic increase in systemic arterial pressure does not per se *result in depression of the basal inotropic state of the left ventricle.*

There is considerable controversy concerning myocardial performance in hypertrophied states. Data derived from in vitro and in vivo experiments as well as available information in human studies suggest that ventricular function is depressed as a result of hypertrophy (Spann *et al.*, 1967, 1969; Bing *et al.*, 1971; Frohlich *et al.*, 1971; Spann *et al.*, 1972; Gunning *et al.*, 1973; Alpert *et al.*, 1974; Mehmel *et al.*, 1975). However, more recent animal experiments suggest that performance is normal in the absence of overt congestive heart failure (Gamble *et al.*, 1973; Malik *et al.*, 1974; Pfeffer *et al.*, 1976; Sasayama *et al.*, 1976). Systemic arterial hypertension is a common cause of left ventricular hypertrophy and in this study we sought to define the functional state of the left ventricle in 18 patients with left ventricular hypertrophy caused by a raised systemic blood pressure. A noninvasive technique, echocardiography, was used to assess left ventricular performance.

Methods

The study group consisted of 9 men and 9 women ranging in age from 21 to 72 years (mean = 48). Of these patients, 8 were black, 4 Mexican-American, and 6 Caucasian. At the time of study, most patients were receiving treatment for high blood pressure. However, no patient was receiving a digitalis glycoside, reserpine, or guanethidine. Other treatment is detailed in the Table. Systolic arterial pressure (cuff method) at the time of study averaged 170 mmHg systolic with a range of 130 to 200 mmHg. Diastolic arterial pressure averaged 104 mmHg with a range of 75 to 140 mmHg. Heart rate averaged 66 beats/min (range 50 to 79). Each patient had left ventricular hypertrophy by the highly specific electrocardiographic criteria described by Romhilt and Estes (1968), by the vectorcardiographic criteria as described by Chou *et al.* (1974), or both. Though two-thirds of our patients had an increased cardiothoracic ratio (>0·5), standard chest radiography was not used to assess left ventricular enlargement because of the substantial number of false positive and false negative results obtained

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Table *Clinical and ultrasound data*

Case No.	*Sex*	*Age (y)*	*HR (bpm)*	*SAP (mmHg)*		*EDD (mm)*	*% ΔD*	*Mean Vcf (diam/s)*	*Vpw* (s^{-1})	*EF (%)*	*Septal thickness*		*PW thickness*	
				S	*D*						*Pre-P (mm)*	*ED (mm)*	*Pre-P (mm)*	*ED (mm)*
1	F	46	72	150	100	42·8	35	1·23	0·78	74	12·6	11·0	16·8	14·6
2	F	21	79	200	140	34·7	39	1·39	0·82	77	7·3	6·3	11·5	11·3
3	F	55	71	200	80	60·0	45	1·33	0·52	83	15·2	13·5	14·6	11·8
4	F	54	72	148	80	45·0	38	1·27	0·91	76	12·0	10·2	11·4	11·4
5	M	39	70	190	135	40·3	40	1·66	1·03	81	15·5	13·5	18·2	13·3
6	M	36	70	200	130	46·4	38	1·15	0·84	75	12·6	12·6	15·1	13·0
7	F	34	71	170	100	43·6	47	1·59	1·13	85	—	—	13·2	11·5
8	F	42	75	165	100	35·7	36	1·38	0·99	74	—	—	14·6	12·4
9	F	54	63	190	110	51·0	50	1·79	1·07	87	10·0	6·6	13·4	11·9
10	M	53	71	200	110	44·9	45	1·54	1·04	91	13·0	11·0	17·2	14·5
11	F	67	50	160	75	40·6	35	1·09	0·81	72	12·5	11·9	16·2	11·8
12	M	50	58	168	105	41·1	37	1·32	0·95	71	14·5	14·6	13·2	14·3
13	F	60	68	160	92	36·8	41	1·28	0·63	80	7·1	9·7	11·4	11·0
14	M	48	56	132	88	52·4	36	1·25	0·68	74	10·6	10·6	13·0	10·6
15	M	43	63	160	110	65·5	28	1·00	0·74	63	17·0	17·0	17·0	15·4
16	M	50	58	130	105	48·4	24	0·86	0·80	61	12·6	12·0	10·5	8·9
17	M	72	63	135	80	51·2	36	1·04	0·62	73	12·6	13·2	15·5	13·6
18	M	34	64	200	130	51·6	20	0·71	0·61	47	19·0	18·2	19·9	17·6
Mean	—	48	66	170	104	46·2	37	1·27	0·83	75	12·7	12·0	14·6	12·7
SE	—	—	1·7	5·9	4·7	1·9	1·8	0·06	0·04	2·4	0·8	0·8	0·6	0·5

SE, standard error; HR, heart rate; SAP, systemic arterial pressure; S, systolic; D, diastolic; EDD, end-diastolic diameter; % ΔD, per cent change in internal diameter; mean Vcf and Vpw: see text; EF, ejection fraction; S/PWT, ratio of septal to posterior wall thickness; h_{ed}/r, ratio of posterior wall thickness to internal radius (EDD/2).

with this method (Glover *et al.*, 1973). It has also been shown that *x*-ray evidence of cardiomegaly was present in only 5 of 112 patients with systemic arterial hypertension who had evidence of left ventricular hypertrophy by ultrasound methods (Drayer *et al.*, 1976).

No patient had a history of previous myocardial infarction or angina pectoris, and none had an intraventricular conduction defect or evidence of previous transmural myocardial infarction on the electrocardiogram. Two patients (cases 16 and 18 in the Table) had recently recovered from an episode of congestive heart failure associated with accelerated hypertension. No other patients had a history of congestive heart failure and none had signs of left ventricular decompensation (pulmonary râles, third heart sound) at the time of study. To obtain this group of 18 patients who met criteria for inclusion into the study, 200 patients attending a hypertension clinic were carefully screened.

Echocardiograms were obtained in the basal state using a Picker Ultrasonoscope employing a 2·25 MHz transducer focused at 7·5 cm with a repetition rate of 1000 impulses/s. The output signal was recorded on a Honeywell Visicorder Oscillograph (model 1856) at a paper speed of either 50 or 100 mm/s. Echocardiograms were obtained with the subjects in the partial left lateral decubitus position. The ultrasound beam was directed so that simultaneous recordings of the endocardial surfaces of

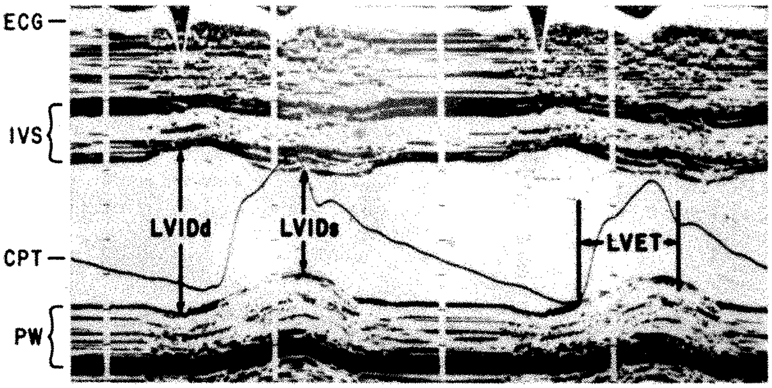

Fig. *The left ventricular dimensions used for calculation of ejection phase indices are illustrated. ECG, electrocardiogram; IVS, interventricular septum; PW, posterior wall; CPT, carotid pulse tracing; LVET, left ventricular ejection time; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole.*

S/PWT (Pre-P)	h_{ed}/r	*Wall stress (g/cm²)*	*Drugs*		
			α-methyldopa	*Thiazide*	*Other*
0·75	0·68	128	—	—	—
0·63	0·65	188	+	+	—
1·03	0·39	178	—	—	Clonidine, frusemide
1·05	0·51	138	+	—	—
0·85	0·66	179	+	—	—
0·83	0·56	203	—	+	—
—	0·53	177	—	—	—
—	0·69	126	+	+	—
0·75	0·47	206	+	+	—
0·76	0·65	149	—	—	—
0·77	0·59	113	+	+	—
1·1	0·69	132	+	+	—
0·62	0·60	142	+	+	—
1·0	0·82	198	—	+	Propranolol
1·0	0·47	205	+	—	Hydrallazine
1·2	0·37	250	+	+	—
0·81	0·53	132	—	+	Triamterene
0·95	0·68	167	+	+	—
0·95	0·56	167			
0·05	0·03	8·7			

the interventricular septum and the posterior left ventricular wall were obtained immediately below the plane of the free edges of the mitral valve (Hirshleifer *et al.*, 1975), (Figure), using the 'standard interspace' method described by Popp *et al.* (1975). No patient had paradoxical septal motion (Hagan *et al.*, 1974). The left ventricular internal dimension at end-diastole was measured at a point on the time motion scan coincident with the R wave of the electrocardiogram. The left ventricular internal dimension at end-systole was defined as the smallest distance separating the left ventricular endocardial surfaces even if the points of maximum excursion were not exactly opposed. The left ventricular ejection time was measured using a simultaneously obtained carotid arterial pulse tracing. Diastolic posterior left ventricular wall thickness and interventricular septal thickness were measured at the onset of the P wave and at the peak of the R wave.

For each patient calculations of ejection phase indices of left ventricular performance were derived using the average of the measurements from five beats in each instance. The mean normalised rate of internal diameter shortening (mean Vcf) was calculated by subtracting the end-systolic diameter from the end-diastolic diameter and dividing the result by the ejection time and the end-diastolic diameter (Karliner *et al.*, 1971b, 1974). The per cent change of internal diameter shortening was also calculated. Mean normalised posterior wall velocity (Vpw) was derived by measuring posterior wall excursion in cm/s and dividing by the ejection time and the end-diastolic diameter (Quinones *et al.*, 1974; Hirshleifer *et al.*, 1975). Ejection fraction was calculated as the ratio of stroke volume to end-diastolic volume using the method of Pombo *et al.* (1971).

To substantiate further the presence of concentric left ventricular hypertrophy, the ratio of wall thickness to end-diastolic radius (h_{ed}/r) was calculated in each patient. It has previously been shown that an increase in this ratio occurs in the presence of concentric left ventricular hypertrophy (Grossman *et al.*, 1975).

Since accurate measurements of end-diastolic dimensions, wall thickness, and systemic diastolic pressure were available, these values were used for the estimation of left ventricular wall stress employing an ellipsoid model (Karliner *et al.*, 1971b). It has been reported by Ratshin *et al.* (1974) that this echocardiographic method of estimating wall stress correlates well with angiographic techniques.

Results

(1) MEASUREMENTS OF WALL THICKNESS

Left ventricular posterior wall thickness measured at the onset of the P wave of the electrocardiogram averaged 14·6±0·6 (SE) mm. In 17 of 18 patients this value exceeded 11 mm, which is the upper limit of normal in our laboratory and is in agreement with previously published values (Feigenbaum, 1972; Henry *et al.*, 1973). Interventricular septal thickness measured at the onset of the P wave averaged 12·7±0·8 mm. This value exceeded the normal upper limit of 11 mm in 12 of 16 patients in whom it was measured. Similar results were obtained when wall thickness was measured at end-diastole (Table). Thus, all patients with left ventricular hypertrophy by electrocardiogram or vectorcardiogram also had either increased left ventricular posterior or interventricular septal wall thickness or both by ultrasound. The ratio of interventricular septal to left ventricular posterior wall thickness at the onset of the P wave was normal in all patients in whom it was measured, and ranged from 0·62 to 1·20.

(2) EJECTION PHASE INDICES OF LEFT VENTRICULAR PERFORMANCE

Mean Vcf in the basal state averaged 1·27±0·06 diameters (diam) s^{-1} and ranged from 0·71 to 1·79 diam s^{-1}. The mean Vcf of only 2 patients fell below the lower limits of normal which in our laboratory is 1·00 diam s^{-1}. Mean Vpw averaged 0·83±0·04 s^{-1} with a range of 0·52 to 1·13 s^{-1}. All patients had values which were within the normal range for our laboratory. Ejection fraction averaged $75 \pm 2{\cdot}4$ per cent with a range of 47 to 91 per cent. Only 3 patients had reduced values ($<67\%$). The change in internal diameter averaged $37 \pm 1{\cdot}8$ per cent, with a range of 20 to 50 per cent, and only 2 patients had reduced values for this measure ($<28\%$). The end-diastolic diameter was normal in all but 2 patients (<56 mm).

(3) ULTRASOUND ASSESSMENT OF CONCENTRIC HYPERTROPHY

The average ratio of wall thickness to end-diastolic radius (h_{ed}/r) was $0{\cdot}56 \pm 0{\cdot}03$. This value is significantly greater than that observed in 29 normal subjects recently studied in our laboratory ($0{\cdot}34 \pm 0{\cdot}02$, $P < 0{\cdot}00001$, unpaired t test).

(4) WALL STRESS

Wall stress in the 18 patients with left ventricular hypertrophy averaged $167 \pm 8{\cdot}7$ g/cm^2. This value did not differ significantly from that obtained in 29 normal subjects recently studied in our laboratory under basal conditions ($172 \pm 6{\cdot}6$ g/cm^2).

Discussion

The results of the present study indicate that in the majority of patients with left ventricular hypertrophy caused by systemic arterial hypertension, the mechanical performance of the hypertrophied heart in the basal state remains within the normal range. Only 3 of the 18 patients had depressed values for ejection phase indices of left ventricular performance and 2 of these (cases 16 and 18) had recently recovered from an episode of congestive heart failure resulting from accelerated hypertension.

PREVIOUS STUDIES IN PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

Much of the evidence concerning the mechanical performance of the nonfailing, hypertrophied myocardium is conflicting, and little information is available from previous studies in human subjects. Toshima *et al.* (1975) reported a normal echocardiographic ejection fraction in 11 patients with concentric left ventricular hypertrophy caused by systemic arterial hypertension. By contrast, Frohlich and his colleagues (1971) described a reduction in resting cardiac output, stroke index, and left ventricular ejection rate in hypertensive patients with left ventricular hypertrophy. In a study using systolic time intervals to assess left ventricular performance, Dodek *et al.* (1975) concluded that a substantial proportion of patients with untreated hypertension had impaired left ventricular performance. In patients with aortic stenosis without heart failure, a depression in left ventricular 'contractility' as measured by isovolumic indices has been reported (Spann *et al.*, 1969; Simon *et al.*, 1970). However, the accuracy of such measurements of left ventricular performance has recently been questioned (Karliner *et al.*, 1974). Since one of the adaptations to a chronic increase in afterload is an increase in muscle mass, i.e. an increase in the number of sarcomeres within cells (Bishop, 1971), we have evaluated left ventricular performance using ejection phase indices normalised per unit of circumference. Such measures should detect basal depression of inotropic state after the adaptation to a chronic increase in afterload has occurred (Sasayama *et al.*, 1976).

EXPERIMENTAL STUDIES OF VENTRICULAR HYPERTROPHY

Although it is generally accepted that experimentally induced chronic volume overload that does not result in overt congestive cardiac failure does not lead to a depression of left ventricular performance (Cooper *et al.*, 1973; Ross, 1974), there is considerable controversy concerning ventricular performance in experimentally induced chronic pressure overload. In studies using isolated papillary muscle preparations, it was concluded that the induction of ventricular hypertrophy led to a depression of the contractile state of the myocardium (Spann *et al.*, 1967; Bing *et al.*, 1971; Spann *et al.*, 1972; Gunning *et al.*, 1973; Alpert *et al.*, 1974). In a more recent study, however, Williams and Potter (1974) showed that, while myocardial depression did occur early (6 weeks) after pulmonary artery banding, the contractile state of papillary muscles removed from cats that survived 24 weeks was normal. These investigators concluded that a depressed contractile state was not a fundamental characteristic of pressure-induced hypertrophy. Recent experiments (Pfeffer and Frohlich, 1973; Malik *et al.*, 1974; Sasayama *et al.*, 1976) tend to support these conclusions, and are in agreement with our own observations in hypertensive patients with left ventricular hypertrophy. Thus, the majority of our patients were in the stable stage (Meerson stage II (Meerson, 1969)) of hypertension which has been shown in the conscious dog with aortic constriction (Sasayama *et al.*, 1976) as well as in the spontaneously hypertensive rat (Pfeffer *et al.*, 1976). Whether acutely induced alterations in heart rate and systemic arterial pressure would detect abnormalities of left ventricular performance not observed in the basal state is open to question. However, we did not feel justified in producing acute alterations in haemodynamics in patients whose systemic arterial pressure was already raised.

CONSIDERATIONS REGARDING WALL STRESS

One explanation of why left ventricular performance was in the normal range in most of our patients with left ventricular hypertrophy is that a compensatory increase in wall thickness reduces wall stress and so permits the left ventricle to shorten against a relatively normal afterload. In 1960, Linzbach proposed that hypertrophy was a compensatory mechanism that increased until the force generated per cross-sectional unit of left ventricular wall returned to normal values. We used the available ultrasound measurements of end-diastolic dimentions, wall thickness, and systemic diastolic pressure to estimate left ventricular wall stress using an ellipsoid model (Karliner *et al.*, 1971b). In support of the use of these measurements to estimate wall stress, it should be pointed out that minimal alterations in left ventricular dimensions occur during isovolumic systole (Karliner *et al.*, 1971a), and that we were unable to detect any significant alterations in wall thickness during isovolumic contractions by echocardiography. As indicated earlier, this echocardiographic method of estimating wall stress correlates well with angiocardiographic techniques (Ratshin *et al.*, 1974).

We are aware, however, that there are certain assumptions underlying such calculations of wall stress. The stresses calculated by the LaPlace formula or any of its variations represent mean values across the thickness of the wall. As Hood *et al.* (1968) have pointed out, the mean value underestimates maximal stress, which occurs toward the endocardial layers, and overestimates minimal stress, which occurs toward the epicardial layers. Moreover, it was not possible to estimate either end-diastolic or peak stress, since our study was a noninvasive one, and measurements of intracavitary left ventricular pressures were not available. Nevertheless, the observation that wall stress values obtained at approximately the time of aortic valve opening (systemic diastolic pressure) do not differ from values obtained in normal subjects provides one explanation of why left ventricular performance may remain normal in the face of a chronic increase in systemic arterial pressure. These observations are also in agreement with the hypothesis of Grossman *et al.* (1975) who proposed that hypertrophy develops to normalise systolic wall stress. In addition, the latter investigators noted that peak wall stress values in patients with concentric left ventricular hypertrophy caused by chronic pressure overload resulting from aortic stenosis also did not differ from values obtained in normal subjects.

ASSESSMENT OF CONCENTRIC HYPERTROPHY

The average ratio of wall thickness to end-diastolic radius (h_{ed}/r) was 0·56, which is almost identical to the value recently reported in patients with chronic pressure overload caused by aortic valvular stenosis (Grossman *et al.*, 1975). As indicated in the Results section, this value significantly exceeded average values in 29 normal subjects. Such an increase in h_{ed}/r is further evidence in favour of the presence of concentric left ventricular hypertrophy in our patients, and is characteristic of the adaptation of the left ventricular chamber to a chronic pressure overload (Levine *et al.*, 1963; Grant *et al.*, 1965; Simon *et al.*, 1970).

CONSIDERATION OF DRUG THERAPY

We recognise that at the time of study many of our patients were receiving drugs which could influence extracellular volume, peripheral resistance, and cardiac output, alone or in combination. Because of the clinical circumstances under which the study was conducted, however, it was not possible to withhold antihypertensive treatment. Nevertheless, inspection of the Table reveals that in the 3 patients who were receiving no treatment at the time of study, left ventricular performance was normal and values did not differ from the other treated patients with normal left ventricular function. Further, the one patient who was receiving propranolol, in whom some depression of cardiac function might have been expected, also had normal left ventricular performance. It should also be emphasised that despite anti-hypertensive treatment in the majority of patients, concentric hypertrophy was present in all.

RELATION OF SYSTEMIC ARTERIAL HYPERTENSION TO CARDIAC DECOMPENSATION

Finally, it is well known that systemic arterial hypertension is a common cause of congestive cardiac failure. Our data are consistent with a recently advanced hypothesis that the heart with a sufficient basal level of contractility can compensate for a chronic pressure overload by hypertrophy to maintain a normal mean Vcf, i.e. normal mechanical performance per unit of circumference. However, when all reserve mechanisms, including hypertrophy and the Frank-Starling mechanism, are maximally used, a further increase in afterload may produce a 'mismatch' between afterload and contractility (Ross, 1976), and thus lead to congestive cardiac failure.

References

Alpert, N. R., Hamrell, B. B., and Halpern, W. (1974). Mechanical and biochemical correlates of cardiac hypertrophy. *Circulation Research,* **34** and **35,** Suppl. 2, 71–82.

Bing, O. H. L., Matsushita, S., Fanburg, B. L., and Levine, H. J. (1971). Mechanical properties of rat cardiac muscle during experimental hypertrophy. *Circulation Research,* **28,** 234–245.

Bishop, S. P. (1971). Ultrastructural alterations in canine myocardial hypertrophy. In *Cardiac Hypertrophy,* pp. 107–124. Ed. by N. P. Alpert. Academic Press, New York.

Chou, T-C., Helm, R. A., and Kaplan, S. (1974). (Eds.) *Clinical Vectorcardiography,* 2nd ed., pp. 71–84. Grune and Stratton, New York.

Cooper, G., IV, Puga, F. J., Zujko, K. J., Harrison, C. E., and Coleman, H. N., III (1973). Normal myocardial function and energetics in volume-overload hypertrophy in the cat. *Circulation Research,* **32,** 140–148.

Dodek, A., Burg, J. R., and Kloster, F. E. (1975). Systolic time intervals in chronic hypertension: alterations and response to treatment. *Chest,* **68,** 51–55.

Drayer, J. I. M., Savage, D. D., Henry, W. L., Mathews, E. C., Laragh, J. H., and Epstein, S. H. (1976). Incidence of echocardiographic left ventricular hypertrophy and left atrial enlargement in essential hypertension (abstract). *Circulation,* **53** and **54,** Suppl. II, 233.

Feigenbaum, H. (1972). *Echocardiography,* p. 216. Lea and Febiger, Philadelphia.

Frohlich, E. D., Tarazi, R. C., and Dustan, H. P. (1971). Clinical-physiological correlations in the development of hypertensive heart disease. *Circulation,* **44,** 446–455.

Gamble, W. J., Phornphutkul, C., Kumar, A. E., Sanders, G. L., Manasek, F. J., and Monroe, R. G. (1973). Ventricular performance, coronary flow, and MV_{O_2}, in aortic coarctation hypertrophy. *American Journal of Physiology,* **224,** 877–883.

Glover, L., Baxley, W. A., and Dodge, H. T. (1973). A quantitative evaluation of heart size measurements from chest roentgenograms. *Circulation,* **47,** 1289–1296.

Grant, C., Greene, D. G., and Bunnell, I. L. (1965). Left ventricular enlargement and hypertrophy. A clinical and angiocardiographic study. *American Journal of Medicine,* **39,** 895–904.

Grossman, W., Jones, D., and McLaurin, L. P. (1975). Wall stress and patterns of hypertrophy in the human left ventricle. *Journal of Clinical Investigation,* **56,** 56–64.

Gunning, J. F., Cooper, G., IV, Harrison, C. E., and Coleman, H. N., III (1973). Myocardial oxygen consumption in experimental hypertrophy and congestive heart failure due to pressure overload. *American Journal of Cardiology,* **32,** 427–436.

Hagan, A. D., Francis, G., Sahn, D., Karliner, J. S., Friedman, W., and O'Rourke, R. A. (1974). Ultrasound evaluation of systolic anterior septal motion in patients with and without ventricular volume overload. *Circulation,* **50,** 248–254.

Henry, W. L., Clark, C. E., and Epstein, S. E. (1973). Asymmetric septal hypertrophy. Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circulation,* **47,** 225–233.

Hirshleifer, J., Crawford, M., O'Rourke, R. A., and Karliner, J. S. (1975). Influence of acute alterations in heart rate and systemic arterial pressure on echocardiographic measures of left ventricular performance in normal human subjects. *Circulation,* **52,** 835–841.

Hood, W. P., Jr., Rackley, C. E., and Rolett, E. L. (1968). Wall stress in the normal and hypertrophied human left ventricle. *American Journal of Cardiology,* **22,** 550–558.

Karliner, J. S., Bouchard, R. J., and Gault, J. H. (1971a). Dimensional changes of the human left ventricle prior to aortic valve opening. *Circulation,* **44,** 312–322.

Karliner, J. S., Gault, J. H., Eckberg, D., Mullins, C. B., and Ross, J., Jr. (1971b). Mean velocity of fibre shortening: a simplified measure of left ventricular myocardial contractility. *Circulation,* **44,** 323–333.

Karliner, J. S., Peterson, K. L., and Ross, J., Jr. (1974). Myocardial mechanics. In *Cardiac Catheterization and Angiography,* pp. 293–303. Ed. by W. Grossman. Lea and Febiger, Philadelphia.

Levine, N. D., Rockoff, S. D., and Braunwald, E. (1963). An angiocardiographic analysis of the thickness of the left ventricular wall and cavity in aortic stenosis and other valvular lesions. *Circulation,* **28,** 339–345.

Linzbach, A. J. (1960). Heart failure from the point of view of quantitative anatomy. *American Journal of Cardiology,* **5,** 370–382.

Malik, A. B., Abe, T., O'Kane, H. O., and Geha, A. S. (1974). Cardiac performance in ventricular hypertrophy induced by pressure and volume overloading. *Journal of Applied Physiology,* **37,** 867–874.

Meerson, F. (1969). The myocardium in hyperfunction, hypertrophy and heart failure. *Circulation Research,* **24-25,** Suppl. II, 1–163.

Mehmel, H. C., Mazzoni, S., and Krayenbuehl, H. P. (1975). Contractility of the hypertrophied human left ventricle in chronic pressure and volume overload. *American Heart Journal,* **90,** 236–240.

Pfeffer, M. A., and Frohlich, E. D. (1973). Hemodynamic and myocardial function in young and old normotensive and spontaneously hypertensive rats. *Circulation Research,* **32** and **33,** Suppl. I, 28–38.

Pfeffer, M. A., Pfeffer, J. M., and Frohlich, E. D. (1976). Pumping ability of the hypertrophying left ventricle of the spontaneously hypertensive rat. *Circulation Research,* **38,** 423–429.

Pombo, J. F., Troy, B. L., and Russell, R. O., Jr. (1971). Left ventricular volumes and ejection fraction by echocardiography. *Circulation,* **43,** 480–490.

Popp, R. L., Filly, K., Brown, O. R., and Harrison, D. C. (1975). Effect of transducer placement on echocardiographic measurement of left ventricular dimensions. *American Journal of Cardiology,* **35,** 537–540.

Quinones, M. A., Gaasch, W. H., and Alexander, J. K. (1974). Echocardiographic assessment of left ventricular function. With special reference to normalized velocities. *Circulation,* **50,** 42–51.

Ratshin, R. A., Rackley, C. E., and Russell, R. O., Jr. (1974). Determination of left ventricular preload and afterload by quantitative echocardiography in man: calibration of the method. *Circulation Research,* **34,** 711–718.

Romhilt, D. W., and Estes, E. H. (1968). A point-score system for the ECG diagnosis of left ventricular hypertrophy. *American Heart Journal,* **75,** 752–758.

Ross, J., Jr. (1974). Adaptations of the left ventricle to chronic volume overload. *Circulation Research,* **34** and **35,** Suppl. II, 64–70.

Ross, J., Jr. (1976). Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. *Progress in Cardiovascular Diseases,* **18,** 255–264.

Sasayama, S., Ross, J., Jr., Franklin, D., Bloor, C. M., Bishop, S., and Dilley, R. B. (1976). Adaptations of the left ventricle to chronic pressure overload. *Circulation Research,* **38,** 172–178.

Simon, H., Krayenbuehl, H. P., Rutishauser, W., and Preter, B. O. (1970). The contractile state of the hypertrophied left ventricular myocardium in aortic stenosis. *American Heart Journal,* **79,** 587–602.

Spann, J. F., Jr., Buccino, R. A., Sonnenblick, E. H., and Braunwald, E. (1967). Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure. *Circulation Research*, **21**, 341–354.

Spann, J. F., Jr., Covell, J. W., Eckberg, D. L., Sonnenblick, E. H., Ross, J., Jr., and Braunwald, E. (1972). Contractile performance of the hypertrophied and chronically failing cat ventricle. *American Journal of Physiology*, **223**, 1150–1157.

Spann, J. F., Jr., Mason, D. T., and Zelis, R. F. (1969). The altered performance of the hypertrophied and failing heart. *American Journal of the Medical Sciences*, **258**, 291–303.

Toshima, H., Koga, Y., Yoshioka, H., Akiyoshi, T., and Kimura, N. (1975). Echocardiographic classification of hypertensive heart disease. A correlative study with clinical features. *Japanese Heart Journal*, **16**, 377–393.

Williams, J. F., Jr., and Potter, R. D. (1974). Normal contractile state of hypertrophied myocardium after pulmonary artery constriction in the cat. *Journal of Clinical Investigation*, **54**, 1266–1272.

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Coarctation of aorta with special reference to infants

Long-term results of operation in 126 cases

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A review of 126 cases of coarctation of the aorta confirms the need for surgical resection in infants with intractable congestive cardiac failure. The high association with additional cardiovascular abnormalities in patients presenting in early infancy contributes significantly to the mortality. Patients with large ventricular septal defects and coarctation of the aorta are at risk and may require pulmonary artery banding at the time of resection of the aortic coarctation. Long-term complications include restenosis (18 cases) and persistent hypertension (10 cases). In order to prevent persistent hypertension, it is suggested that elective resection of the coarctation be done at 1 year of age.

Coarctation of the aorta accounts for 5 to 8 per cent of congenital cardiac anomalies (Keith *et al.*, 1967; Nadas and Fyler, 1972). When babies with coarctation of the aorta present with intractable congestive cardiac failure, there is frequently an associated cardiovascular anomaly (Kempton and Waterson, 1957; Tawes *et al.*, 1969; Becker *et al.*, 1970). The response to intensive medical treatment is often disappointing (Mortensen *et al.*, 1959; Chang and Burrington, 1972), but is most satisfactory in children with uncomplicated coarctation (Lang and Nadas, 1956).

Calodney and Carson (1950) and Kirklin *et al.* (1952) reported the first 2 infants undergoing successful surgical repair for coarctation of the aorta. Recent publications suggest that operation is preferred to medical treatment in infants with refractory congestive cardiac failure (Sinha *et al.*, 1969; Tawes *et al.*, 1969; Chang and Burrington, 1972; Weldon and Hartmann, 1974). Though the results in survivors are excellent, there still remains the problem of recurrence of aortic coarctation in some cases (Kempton and Watertson, 1957; Mulder and Linde, 1959; Parsons and Astley, 1966; Khoury and Hawes, 1968; Hartmann *et al.*, 1970).

Patients

The purpose of this paper is to analyse our experience with 126 patients, including 61 infants, treated surgically for coarctation of the aorta between April 1961 and October 1972. Patients with hypoplastic left heart syndrome, where the aortic coarctation played a minor role in haemodynamics, have been excluded. The age at which the condition presented ranged from 6 days to 14 years (Fig. 1). Sixty-one cases less than 1 year old will be considered separately from older children.

GROUP 1: 61 INFANTS

There were 34 boys and 27 girls; 79 per cent were less than 6 weeks old at the time of operation, and all were extremely ill with signs of congestive cardiac failure (Table 1). Most infants required feeding by an indwelling intragastric tube. Absent or diminished femoral pulses and a non-specific cardiac murmur were the most consistent signs. Cyanosis was observed in 42 per cent but differential cyanosis was not a reliable sign of preductal coarctation.

Electrocardiogram showed right ventricular hypertrophy in 62 per cent of infants (Table 2). This finding was consistent with associated pulmonary hypertension or increased pulmonary vascular resistance. Pure left ventricular hyper-

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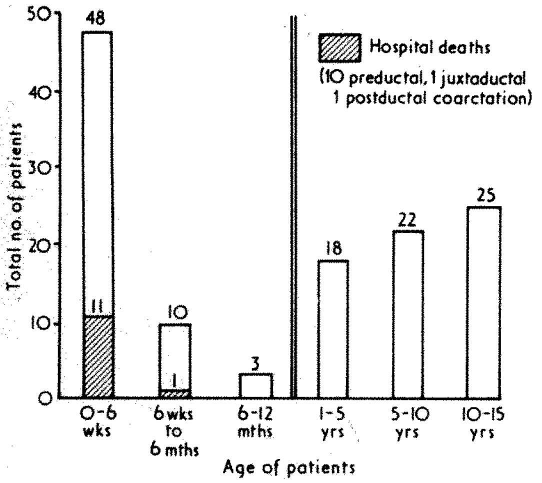

Fig. 1 *Distribution of age and mortality in 126 cases of coarctation of the aorta.*

trophy was seen in 7 cases, and ST depression and T wave inversion in leads V5 to V6 were recorded in 6 patients, including 3 patients later found to have endocardial fibroelastosis.

Chest *x*-ray films showed cardiomegaly in 68 per cent of cases. Evidence of increased pulmonary vascularity was frequently observed, but it was difficult to be confident about the presence of pulmonary venous congestion.

Angiocardiogram and cardiac catheterisation were carried out if additional cardiac anomalies were suspected. Venous angiocardiogram was performed in 21 patients, and cardiac catheterisation in 34 patients: 4 patients had both procedures. In addition to the coarctation, a persistent ductus arteriosus was found in 53 patients, ventricular septal defect in 22 patients, and aortic stenosis in 10 patients. The frequency and combination of these and other lesions have been set out in Table 3. Extracardiac abnormalities included tracheo-oeso-

Table 1 *Presenting symptoms and signs in infants and children with coarctation of aorta*

	Infants (%)	*Children* (%)
Difficulty with feeding	72	—
Dyspnoea	78	8
Central cyanosis	42	2
Poor weight gain	70	16
Hepatomegaly	90	12
Cardiomegaly	68	36
Decreased or absent femoral pulses	89	78
Cardiac murmur	82	92
Hypertension	?	58
Rib notching	—	14

Table 2 *Electrocardiographic data in 126 cases, with coarctation of aorta*

	Infants	*Children*
Right ventricular hypertrophy	38	4
Combined ventricular hypertrophy	13	3
Left ventricular hypertrophy	7	37
Normal	3	21
Total	61	65
ST and T wave changes	6	8

Table 3 *Associated cardiovascular lesions and early deaths in 126 cases with coarctation of aorta*

	Infants (61)	*Deaths*	*Children (65)*
Persistent ductus arteriosus	19	1	13
Ventricular septal defect + persistent ductus arteriosus	13	1	5
Ventricular septal defect	—	—	2
Ventricular septal defect + persistent ductus arteriosus + aortic stenosis	2	2	—
Persistent ductus arteriosus + aortic stenosis	4	—	1
Ventricular septal defect + persistent ductus arteriosus + hypoplastic aortic arch	3	3	—
Endocardial fibroelastosis + aortic stenosis	2	—	—
Endocardial fibroelastosis + aortic stenosis + persistent ductus arteriosus	2	2	2
Endocardial fibroelastosis + persistent ductus arteriosus	1	—	—
Endocardial cushion defect + persistent ductus arteriosus	2	1	—
Atrial septal defect + persistent ductus arteriosus	1	—	—
Mitral regurgitation + mitral stenosis	6	—	2
D-transposition of great arteries + ventricular septal defect + persistent ductus arteriosus	2	1	—
Taussig-Bing + ventricular septal defect + persistent ductus arteriosus	2	1	—
Persistent ductus arteriosus + pulmonary stenosis	1	—	—
Aortic stenosis	—	—	3
Ebstein's anomaly	—	—	1
Atrial septal defect	1	—	—
Total	61	12	29

Table 4 *Type of operation in 126 cases with coarctation of aorta*

	Infants	*Children*
End-to-end anastomosis	52	50
Prosthetic grafts	4	12
Left subclavian split longitudinally	5	—
End-to-side anastomosis	—	1
Left subclavian to descending aorta	—	2
Total	61	65
Pulmonary artery constriction	14	—

phageal fistulae (2 cases), hydrocephalus (1 case), and Turner's syndrome (1 case).

Treatment with digoxin, frusemide, and oxygen was given to all the patients for at least 24 to 48 hours before considering operation, without which survival seemed extremely unlikely.

Operation

A left lateral thoracotomy was performed in the third or fourth intercostal spaces. Cross-clamping of the aorta was required for 8 to 20 minutes. The coarcted segment was resected, and a persistent ductus ligated when present. End-to-end anastomosis was possible in most cases (Table 4). Continuous suture (5/0 or 6/0 silk) was used in 27 patients, while in the remainder interrupted silk was used. A pericardial graft was inserted in 4 patients with aortic arch hypoplasia and the left subclavian artery was split longitudinally to facilitate end-to-end anastomosis in 5 cases.

Pulmonary artery constriction was necessary in patients with ventricular septal defect (6 cases), transposition of great arteries (2 cases), and Taussig-Bing complex (2 cases). This procedure was performed after resection of the coarctation of the aorta. Four other patients with ventricular septal defects did not improve and required pulmonary artery constriction subsequently.

Coarctation was classified in relation to ductus arteriosus or ligamentum arteriosum according to the surgeon's sketch of his operative findings. Most of the infants had coarctation at or above the ductus or ligamentum arteriosum (Table 5).

During the postoperative period there was an immediate improvement in 40 patients (66%). Nineteen patients, however, did not improve and required digoxin and frusemide. Prolonged ventilation was necessary in 8 patients—4 of whom required tracheostomy.

Femoral arterial pulses were palpable after the operation in all patients and there was no doubt in the surgeon's mind that an adequate anastomosis was performed. In 2 patients within 48 hours of operation, however, congestive cardiac failure persisted and the femoral pulses were absent: coarctation had recurred and a second resection was required. Histological examination of the resected segment showed damage to the internal layer with clotting over the suture line.

Table 5 *Types of coarctation of aorta*

	Infants	*Children*
Preductal	26	4
Juxtaductal	26	12
Postductal	1	6
Preligamental	2	5
Juxtaligamental	4	26
Postligamental	0	12
Difficult to classify	2	—
Total	61	65

Table 6 *Postoperative complications*

	Infants (61)	*Children (65)*
Pulmonary	8	5
Haemorrhage	1	3
Hypertension	12	16
Abdominal pain	?	5
Ventricular fibrillation	5	—
Renal failure	6	—
Hemiplegia	—	1
Aortic arch aneurysm	—	1
Spinal cord	—	—
Restenosis	15	3
Persistent hypertension without restenosis	2	8

The postoperative complications are listed in Table 6. Restenosis of the aorta was the commonest complication. This occurred over a variable period from 2 days to 4 years and will be discussed later. Pulmonary complications were the result of major atelectasis or pneumonia. Persistent (paradoxical) hypertension occurred in 12 infants. Renal failure occurred in 6 patients—all of whom were extremely ill before operation.

Results

There were 12 hospital deaths (Fig. 1). All these cases had associated cardiovascular anomalies (Table 3). Ventricular fibrillation was responsible for 3 deaths—2 during operation and 1 three weeks after resection of coarctation of the aorta. A patient with associated severe aortic stenosis remained in congestive cardiac failure and died 4 weeks later after aortic valvotomy. Renal failure contributed to 4 deaths. Endocardial fibroelastosis was present in 3 instances at necropsy. There were 3 late deaths in this group (Table 7). A patient with pulmonary artery constriction died of haemorrhage caused by rupture of a pulmonary artery aneurysm, as a result of the band cutting through. This case has been described previously (Patel *et al.*, 1973). Two other late deaths occurred in patients with recurrence of coarctation of the aorta, 1 as a result of pneumonia after successful resection of the recoarctation and another as a result of gastroenteritis.

GROUP 2: 65 OLDER CHILDREN

Sixty-five children (30 boys and 35 girls) from 1 to 14 years of age underwent resection of the coarctation of the aorta (Fig. 1). Only 7 patients were in con-

Table 7 *Coarctation of aorta: late deaths*

Case No.	*Age at operation*	*Associated cardiac lesion*	*Cause of death*	*Interval after operation*
1	2 w	Persistent ductus arteriosus + aortic stenosis	Pneumonia, recoarctation	2 mth
2	3 mth	Ventricular septal defect + persistent ductus arteriosus	Aneurysm of pulmonary artery*	7 mth
3	4 w	Ventricular septal defect + persistant ductus arteriosus	Gastroenteritis	6 mth
4	4 y	Double coarctation	Aneurysm of aorta	2 y
5	14 y	Ebstein's anomaly	Sudden death ? arrhythmia	3 y

*Pulmonary artery band cutting through.

gestive cardiac failure. Diminished or absent femoral pulses (78%) and hypertension (58%) were common presenting signs. A cardiac murmur (92%) was often an incidental finding at school health examination (Table 1).

Electrocardiogram showed left ventricular hypertrophy in 37 patients, 8 of whom had evidence of left ventricular strain with ST and T changes in leads V5 to V6 (Table 2). Right ventricular hypertrophy was observed in 4 patients with persistent ductus arteriosus and pulmonary hypertension. Electrocardiogram was interpreted as normal in 21 patients.

Chest radiograph showed cardiac enlargement in 36 per cent. Rib notching was present in 14 per cent, the youngest being 3 years of age and the oldest 14 years. Right and left heart catheterisation was performed in 18 patients. Eight other patients had an aortogram only. The remaining cases were operated upon without any haemodynamic investigations.

The nature of coarctation of the aorta in relation to the ligamentum or ductus arteriosus has been set out in Table 5. Though most cases were at or below the ligamentum or ductus, there were 4 cases with preductal and 5 patients with preligamental coarctation.

Persistent ductus was present in 21 patients. Ventricular septal defect and aortic stenosis were the other common associated cardiac lesions (Table 3). Ebstein's anomaly was present in 1 patient and there were 3 patients with Turner's syndrome.

Operation

This was performed to prevent long-term complications such as hypertension or subarachnoid haemorrhage. It was possible to perform end-to-end anastomosis in 50 patients. Two patients required a left subclavian artery to descending aorta anastomosis, while in 1 patient with a double coarctation an end-to-side anastomosis was performed between descending aorta and the proximal aortic arch (Table 4). Continuous (6/0 silk) suture was used in 26 patients, while in others interrupted stitches were used. In 12 patients, it was necessary to use grafts after resection of the coarctation (1 'dacron', 2 pericardial, and 9 'teflon').

The postoperative course was usually uneventful. Persistent (paradoxical) hypertension occurred in 16 patients, but antihypertensive therapy was required in 3 patients only (Table 6). Five children had abdominal pain accompanied by gastrointestinal bleeding in 2. Mesenteric arteritis was naturally suspected but laparotomy was not necessary. One patient developed right hemiplegia after resection of coarctation of the aorta resulting from thrombosis in the arteriosclerotic carotid artery. This observation was based on aortic arch aortogram.

Results

There were no hospital deaths, but 2 late deaths have occurred in the older group. A patient with Ebstein's anomaly had successful resection of the coarctation at the age of 14 years but died suddenly 3 years later, probably as a result of arrhythmia. The other late death occurred in a patient with double coarctation 2 years after resection of the distal coarctation and end-to-side anastomosis. He died of haemorrhage caused by rupture of the right innominate artery into the oesophagus (Table 7).

Forty infants and 58 children who survived operation have been followed up for 3 to 11 years (mean 6·4 years). Physical growth has been satisfactory even in the patients with restenosis of the aorta. Electrocardiogram and chest radiographs have returned to normal in all except 12 patients. Two survivors with endocardial fibroelastosis have cardiomegaly and left ventricular strain. Aortic valvotomy has been performed in 4 patients from

Table 8 *Restenosis of coarctation of aorta 18 cases (15 infants)*

Age at operation	
0–6 w	12
6 w–6 m	3
1 y–14 y	3
Type of coarctation	
Preductal	11
Juxtaductal	4
Postductal	2
Preligament	1

the infant group and 2 older children. Apart from the proven cases of aortic stenosis, 10 have ejection systolic murmurs (grade 1–2/4) with ejection clicks suggestive of bicuspid aortic valves. They have not yet been fully investigated as they do not have symptoms and the electrocardiograms have been normal.

Out of 14 'infant' survivors with ventricular septal defects, there has been spontaneous closure of the defect in 4, including 1 with pulmonary artery banding. Three other patients with pulmonary artery constriction have now had successful removal of the band and closure of ventricular septal defect. Four patients have had closure of the ventricular septal defect.

Recoarctation occurred in 2 infants within 1 week of operation and between 2 months and 7 years after operation in 16 other infants and children. Recoarctation was more commonly seen in patients with preductal coarctation operated on before the age of 6 weeks (Table 8). There were only 3 cases of restenosis among the children operated upon after the age of 1 year and prosthetic grafts were used in 2 of them (Table 9).

Evidence of recoarctation was provided by cardiac catheterisation in 12 patients from group 1 and 3 patients from group 2. The systolic gradient across the coarctation was measured. The aortic diameter at the level of the coarctation and that at the level of diaphragm was measured and expressed as a ratio. The systolic gradient is plotted against the aortic ratio in Fig. 2. Significant narrowing of the aortic lumen occurred when the ratio was less than 0·5. This occurs more commonly when the gradient is more than 40 mmHg (Fig. 2). Seven patients have subsequently undergone resection of the recoarctation.

Blood pressure measurements were made several years after the initial operation and the results are shown in Fig. 3 and 4. Only the mean of 3 recordings has been plotted. Though patients with recoarctation were generally hypertensive, there are 2 patients from the infant group and 8 patients from group 2 who are hypertensive without any evidence of recoarctation. Their renal function is normal and 6 have raised plasma renin levels. Persistence of hypertension seems to be more common when patients are operated upon at an older age (Fig. 4).

Table 9 *Restenosis of coarctation of aorta 18 cases (15 infants)*

Type of suture	*Infants*	*Children*
Continuous	9	1
Interrupted	6	2
Type of operation		
End-to-end	14	1
Prosthetic graft	1	2

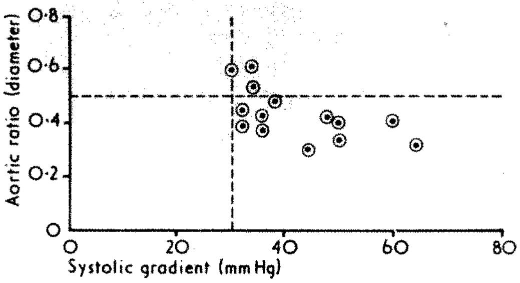

Fig. 2 *Systolic gradient across coarctation at cardiac catheterisation plotted against 'aortic ratio' (diameter of aorta at site of recurrent coarctation/diameter of aorta at diaphragm).*

Discussion

Our clinical material confirms that coarctation of the aorta, presenting with refractory congestive cardiac failure during early infancy, usually has a wide spectrum of associated cardiovascular anomalies. Sinha *et al.* (1969) did not have any survivors in this group with medical management alone. By contrast with surgical treatment there was a 78 per cent survival rate. Recently, Chang and Burrington (1972) and Kilman *et al.* (1972) have also reported a higher success rate with surgical management. Table 10 summarises the experience from a number of centres. Mortality from operation for coarctation of the aorta can usually be attributed to the associated complex cardiovascular anomalies. Tawes *et al.* (1969) observed evidence of myocardial ischaemia in some of the fatal cases. We have not been able to confirm this at necropsy in our cases, but ischaemic changes have been suspected on electrocardiograms in 4 patients.

Litwin *et al.* (1971) reported a higher incidence of pulmonary hypertension, observed during cardiac catheterisation, among their patients who died after operation for coarctation of the aorta. In our experience, there is usually a dramatic improvement after operation, and in most of our survivors congestive heart failure has disappeared within 24 to 48 hours.

Patients with ventricular septal defects and coarctation of the aorta present a dilemma—whether pulmonary artery constriction should be performed at the initial operation. It has been our practice to resect the coarctation before banding the pulmonary artery. We feel that after aortic resection, the left-to-right intracardiac shunt is often reduced and, in some cases, pulmonary artery constriction may not then be necessary. Out of 22 patients with ventricular septal defects, 10 required pulmonary artery banding at the time of resection of the coarctation and a further 4 patients required pulmonary artery constriction later. This additional procedure appears to carry a significantly high risk. The decision to band the pulmonary artery was made after resection of the coarctation. If the pulmonary artery felt tense and there was a thrill, pulmonary artery banding was performed. Criteria for late banding were persistent cardiac failure with

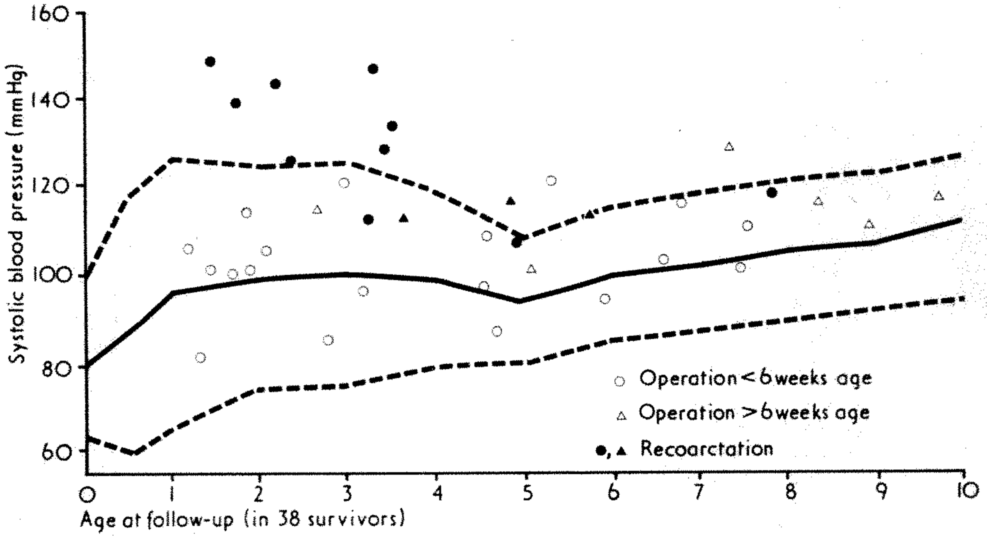

Fig. 3 *Long-term systolic blood pressure after resection of coarctation of the aorta in infants. Continuous line represents the average systolic blood pressure and the stippled line the standard deviation in normal children (Nadas and Fyler, 1972).*

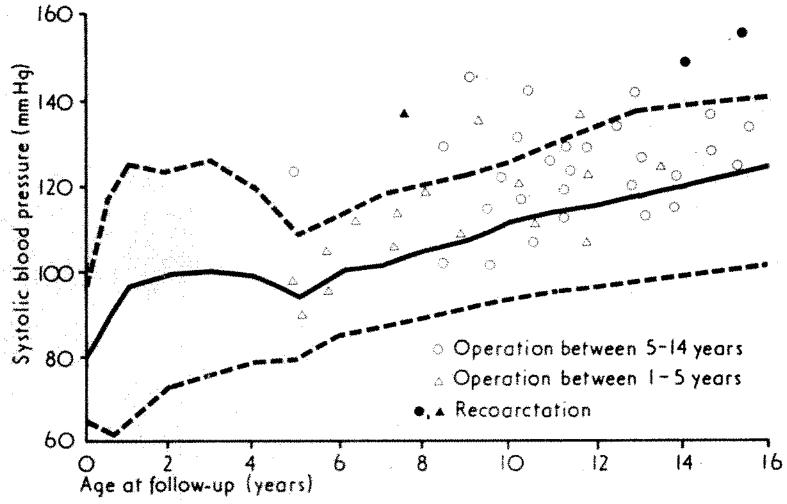

Fig. 4 *Systolic blood pressure in relation to age in children after operation for coarctation of the aorta. Continuous line represents the average systolic blood pressure and the stippled lines the standard deviation in normal children (Nadas and Fyler, 1972).*

Table 10 *Mortality among infants with coarctation of aorta in published series*

Author	*Year*	*Medical*		*Surgical*	
		No.	%	*No.*	%
Mortensen *et al.*	1959	4/8	50	0/8	0
Glass *et al.*	1960	37/74	50	14/34	41
Freundlich *et al.*	1961	12/27	40	3/3	100
Malm *et al.*	1963	—	—	8/32	25
Hartmann *et al.*	1967	—	—	5/15	33
Tawes *et al.*	1969	—	—	81/179	45
Sinha *et al.*	1969	18/26	69	10/28	36
Litwin *et al.**	1971	—	—	14/46	30
Chang and Burrington	1972	33/53	58	30/57	53
Present series		—	—	12/61	20

*Up to 2 years.

evidence of a large left-to-right shunt after successful resection of the coarctation. In 4 patients, the ventricular septal defect has closed spontaneously.

It has, however, been suggested by Weldon and Hartmann (1974) that pulmonary artery constriction should be performed before resection of the coarctation when there is a large intracardiac shunt. The authors claim that by this method left ventricular volume overload is prevented during aortic resection.

Although the long-term results of operation for coarctation of the aorta are satisfactory, about 20 to 30 per cent of the survivors develop recoarctation. The possible causes of restenosis present an interesting problem. We have observed recoarctation within one week of operation in 2 cases; both patients required another operation and there was evidence of clotting over the suture line. Recoarctation in these cases may be attributed to the anastomotic technique. In 16 other patients, however, restenosis developed over a variable period between 2 months to 7 years. Thirteen of these cases were operated upon during infancy.

There have been several reports regarding the growth of the anastomosis in children. Moss *et al.* (1959) reviewed the angiograms of 5 infants 2 to 4 years after aortic resection and found evidence of growth deficiency. Rathi and Keith (1964) reviewed 150 patients after operation and did not find any evidence of recurrent coarctation or of failure of the anastomosis to grow. Pelletier *et al.* (1969), in a careful study of patients operated upon during infancy, observed that effective narrowing of the lumen occurs only when the diameter at the anastomotic site is less than 55 per cent of the aortic diameter at the level of the diaphragm. Our own observations, in 15 cases of recoarctation who had cardiac catheterisation and aortogram, also suggest that narrowing of the aortic lumen ranged from 32 to 48 per cent. Failure of the anastomosis to grow cannot account for recurrent coarctation because we have observed that the aortic lumen in cases of recoarction is, in fact, smaller than that created at the time of operation. Furthermore, recoarctation of the aorta has also been reported in several adult patients (Cerilli and Lauridsen, 1965). Hence, the failure of the anastomosis to grow cannot account for all cases of recoarctation.

The use of continuous suture of the anastomosis has been suggested to be responsible for recoarctation, but we have used both continuous and interrupted stitches and have not found any significant difference in the development of restenosis (Table 9).

Khoury and Hawes (1968) reported on the histological findings in cases of recoarctation. They observed distinct thickening of intima and hypertrophy of the media with disruption of the internal elastic lamina. We have also noted similar findings in 4 of our cases. These changes are similar to those responsible for intimal thickening and medial spur described by Edwards *et al.* (1948). It seems likely that, at the time of resection of the coarctation, some tissue with an inherent tendency to contract is left behind and this may be responsible for recoarctation in some cases.

Berry and Tawes (1970) examined the resected surgical specimens and suggested that an abnormal accumulation of mucopolysaccharides occurred in the media of these cases. The changes were degenerative in nature and the result of hypertension or operation. They postulated that the effect of alteration in mucopolysaccharide component of the vessel wall may lead to restenosis by altering the dynamic behaviour of the vessel.

Persistent hypertension without evidence of recoarctation has previously been reported (Maron *et al.*, 1973; Shinebourne *et al.*, 1976). Hypertension without recoarctation or renal pathology has occurred in 2 patients from group 1 and 8 from group 2. The lower limb blood pressures in these patients are raised in contrast to those with recoarctation. These findings are similar to those described by Shinebourne *et al.* (1976). It seems likely that there is an abnormality of the renin-angiotensin system. We recommend that elective resection of coarctation of the aorta be performed at the age of 1 year, when the incidence of recoarctation and mortality of the operation is low (Fig. 1).

The aortic arch and isthmus is invariably poorly developed in infants with coarctation of the aorta and coexisting cardiovascular lesions, particularly large left-to-right shunts. It is now well established that this anomaly results from reduced aortic flow during intrauterine development (Shinebourne and Elseed, 1974). The isthmal hypoplasia renders the anastomosis, after resection of the coarctation, rather difficult. In order to facilitate the anastomosis, Hamilton *et al.* (1976) have used a left subclavian artery flap aortoplasty with gratifying results. The reported incidence of restenosis after such a reconstruction was only 2 in 23 survivors.

Tawes *et al.* (1969) have suggested that the coronary arteries, in patients with coarctation of the aorta, are frequently abnormal. It is thus likely that persistent hypertension with abnormal coronary blood flow may contribute significantly to premature death from ischaemic heart disease.

References

Becker, A. E., Becker, M. J., and Edwards, J. E. (1970). Anomalies associated with coarctation of aorta. Particular reference to infancy. *Circulation,* **41,** 1067–1075.

Berry, C., and Tawes, R. L., Jr. (1970). Mucopolysaccharides of the aortic wall in coarctation and recoarctation. *Cardiovascular Research,* **4,** 224–227.

Calodney, M. M., and Carson, M. J. (1950). Coarctation of the aorta in early infancy. *Journal of Pediatrics,* **37,** 46–77.

Cerilli, J., and Lauridsen, P. (1965). Reoperation for coarctation of the aorta. *Acta Chirurgica Scandinavica,* **129,** 391–394.

Chang, J. H. T., and Burrington, J. D. (1972). Coarctation of the aorta in infants and children. *Journal of Pediatric Surgery,* **7,** 127–135.

Edwards, J. E., Christensen, N. A., Clagett, O. T., and McDonald, J. R. (1948). Pathologic considerations in coarctation of the aorta. *Proceedings of the Staff Meetings of the Mayo Clinic,* **23,** 324–332.

Freundlich, E., Engle, M. A., and Goldberg, H. P. (1961). Coarctation of the aorta in infancy. Analysis of a 10 year experience with medical management. *Pediatrics,* **27,** 427–440.

Glass, I. H., Mustard, W. T., and Keith, J. D. (1960). Coarctation of the aorta in infants. *Pediatrics,* **26,** 109–121.

Hamilton, D., Shackleton, J., Jones, R. S., Arnold, R., and Wilkinson, J. L. (1976). Surgical correction of coarctation of the aorta (four days to 6½ months) using left subclavian artery flap aortoplasty. In Proceedings of the British Cardiac Society Autumn Meeting, p. 51. (Abstract in *British Heart Journal,* 1977, **39,** 354.)

Hartmann, A. F., Jr., Goldring, D., Hernandez, A., Behrer, M. R., Schad, N., Ferguson, T., and Burford, T. (1970). Recurrent coarctation of the aorta after successful repair in infancy. *American Journal of Cardiology,* **25,** 405–410.

Hartmann, A. F., Jr., Goldring, D., and Staple, T. (1967). Coarctation of the aorta in infancy. Hemodynamic studies. *Journal of Pediatrics,* **70,** 95–104.

Keith, J. D., Rowe, R. D., and Vlad, P. (1957). *Heart Disease in Infancy and Childhood,* 2nd ed. MacMillan, London.

Kempton, J. J., and Waterston, D. J. (1957). Coarctation of aorta presenting as cardiac failure in early infancy. *British Medical Journal,* **2,** 442–444.

Khoury, G. H., and Hawes, C. R. (1968). Recurrent coarctation of the aorta in infancy and childhood. *Journal of Pediatrics,* **72,** 801–806.

Kilman, J. W., Williams, T. E., Breza, T. S., Craenen, J., and Hoseir, D. M. (1972). Reversal of infant mortality by early surgical correction of coarctation of the aorta. *Archives of Surgery,* **105,** 865–868.

Kirklin, J. W., Burchell, H. B., Pugh, D. G., Burke, E. C., and Mills, S. D. (1952). Surgical treatment of coarctation of the aorta in a ten-week-old infant. Report of a case. *Circulation,* **6,** 411–414.

Lang, H. T., Jr., and Nadas, A. S. (1956). Coarctation of the aorta with congestive heart failure in infancy—medical treatment. *Pediatrics,* **17,** 45–57.

Litwin, S. B., Bernhard, W. F., Rosenthal, A., and Gross, R. E. (1971). Surgical resection of coarctation of the aorta in infancy. *Journal of Pediatric Surgery,* **6,** 307–313.

Malm, J. R., Blumenthal, S., Jameson, A. G., and Humphreys, G. H. (1963). Observations on coarctation of the aorta in infants. *Archives of Surgery,* **86,** 96–102.

Maron, B. J., Humphries, J. O'N., Rowe, R. D., and Mellits, E. D. (1973). Prognosis of surgically corrected coarctation of the aorta: a 20 year postoperative appraisal. *Circulation,* **47,** 119–126.

Mortensen, J. D., Cutler, P. R., Rumel, W. R., and Veasy, L. G. (1959). Management of coarctation of the aorta in infancy. *Journal of Thoracic and Cardiovascular Surgery,* **37,** 502–509.

Moss, A. J., Adams, F. H., O'Loughlin, B. J., and Dixon, W. J. (1959). The growth of the normal aorta and of the anastomotic site in infants following surgical resection coartation of the aorta. *Circulation,* **19,** 338–349.

Mulder, D. G., and Linde, L. M. (1959). Recurrent coarctation of the aorta in infancy. *American Surgeon,* **25,** 908–911.

Nadas, A. S., and Fyler, D. C. (1972). *Pediatric Cardiology,* 3rd ed., pp. 452 and 665. Saunders, Philadelphia.

Parsons, C. G., and Astley, R. (1966). Recurrence of aortic coarctation after operation in childhood. *British Medical Journal,* **1,** 573–577.

Patel, R. G., Ibenacho, H. N. C., Abrams, L. D., Astley, R., Parsons, C. G., Roberts, K. D., and Singh, S. P. (1973). Pulmonary artery banding and subsequent repair in ventricular septal defect. *British Heart Journal,* **35,** 651–656.

Pelletier, C., Davignon, A., Ethier, M. F., and Stanley, P. (1969). Coarctation of the aorta in infancy. *Journal of Thoracic and Cardiovascular Surgery,* **57,** 171–179.

Rathi, L., and Keith, J. D. (1964). Postoperative blood pressures in coarctation of the aorta. *British Heart Journal,* **26,** 671–678.

Sinha, S. N., Kardatzke, M. L., Cole, R. B., Muster, A. J., Wessel, H. V., and Paul, M. H. (1969). Coarctation of the aorta in infancy. *Circulation,* **40,** 385–398.

Shinebourne, E. A., and Elseed, A. M. (1974). Relation between fetal flow patterns, coarctation of the aorta and pulmonary blood flow. *British Heart Journal,* **36,** 498–492.

Shinebourne, E. A., Tam, A. S. Y., Elseed, A. M., Paneth, M., Lennox, S. C., Cleland, W. P., Lincoln, C., Joseph, M. C., and Anderson, R. H. (1976). Coarctation of the aorta in infancy and childhood. *British Heart Journal,* **38,** 375–380.

Tawes, R. L., Aberdeen, E., Waterson, D. J., and Bonham-Carter, R. E. (1969). Coarctation of the aorta in infants and children. A review of 333 operative cases including 179 infants. *Circulation,* **39** and **40,** Suppl. I, 173–184.

Weldon, C. S., and Hartmann, A. F., Jr. (1974). Surgical correction of coarctation of the aorta in infancy (abstract). *American Journal of Cardiology,* **33,** 177.

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Cardiovascular anomalies in thoracopagus twins and the importance of preoperative cardiac evaluation

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Four pairs of thoracopagus twins have been described. Cardiac catheterisation was performed in all the cases. Angiocardiographic and necropsy findings suggest that the most common abnormality was some form of univentricular heart. The communication between the 2 hearts was at atrial level in 2 cases. Separation was performed in 1 of these cases but only 1 of the twins survived for 14 hours after operation. It is suggested that full cardiac catheterisation with selective angiocardiogram is essential before separation is considered. Identical heart rates were observed in each pair and there was invariably a major communication between the hearts of the twins.

The incidence of conjoined twins has been estimated at about 1 in 50 000 births (Morrison, 1963; Amiel, 1967). Frequently the twins are born dead but more than 300 cases of survival, from a few hours to 63 years, have been documented (Tandon *et al.*, 1974). Survival depends on the site of union of the twins and the resultant fusion of vital organs. Thoracopagus twins are joined from the anterior part of the thorax down to the umbilicus. Nearly 75 per cent of such twins have serious cardiovascular anomalies which influence the prospects of successful surgical separation (Leachman *et al.*, 1967; Nichols *et al.*, 1967). Ten attempts at surgical separation have been discovered in a review of the reports published since 1925, but there has not been a successful separation in twins sharing a heart or part of it (Mulcare *et al.*, 1970). However, with recent advances in paediatric cardiovascular surgery, it should be possible to separate some of them, and hence it is essential to carry out full preoperative cardiovascular investigation.

The purpose of this communication is to report an attempted surgical separation and to review the cardiovascular abnormalities in 4 pairs of thoracopagus twins seen at The Hospital for Sick Children, London. In all 4, simultaneous electrocardiograms from the twins recorded an identical heart rate, suggesting the association of fused hearts.

Case 1

The twins, both female, were born after an elective lower segment caesarian section at 39 weeks' gestation. The pregnancy was uneventful and there was no history of any ingestion of drugs during pregnancy. The parents were both 29 years old and have one other child—a girl, 2 years old, who is normal. The combined weight of the twins was 4·9 kg. Respiratory difficulty was noticed soon after birth. The twins were intubated and transferred to The Hospital for Sick Children, Great Ormond Street.

On examination, they were joined across the chest and abdomen over a distance of 15 cm. Their facial appearances were normal. There was an infraumbilical hernia with a single umbilical cord containing two umbilical arteries and two umbilical veins. All the peripheral pulses were felt, at a rate of 90 per minute, and simultaneous limb lead electrocardiograms confirmed identical heart rates for the twins. Because of rapid deterioration in the condition of Twin B, cardiac catheterisation was performed and revealed the following.

TWIN A

A distinctly separate inferior vena cava led to the right atrium. The right ventricle was entered from

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the right atrium. The pulmonary artery originated from the right ventricle. Right ventriculography showed a free communication with the (morphological) right ventricular chamber of Twin B. There was a hypoplastic left ventricle giving rise to a hypoplastic aorta.

TWIN B

The right atrium was entered from the inferior vena cava. The same ventricular chamber was entered via two different atrioventricular valves. Ventriculography confirmed a primitive ventricle with a subaortic outlet chamber.

Cardiac arrest occurred soon after the angiocardiogram in Twin B. Despite resuscitative measures, the twins died.

Necropsy confirmed the angiocardiographic findings. In Twin A there was a mitral valve hypoplasia with hypoplastic left ventricle and bicuspid aortic valve. Twin B had a primitive ventricle with two atrioventricular valves and subaortic outlet chamber. There was a free communication between the two 'right' ventricular chambers of the twins.

In addition to the cardiovascular anomalies the small intestines between the duodenum to ileum were fused. There was also continuity between the liver tissue of the twins.

Case 2

The conjoint twins were admitted to The Hospital for Sick Children, Great Ormond Street, in August 1968, immediately after birth. The mother was a primigravida aged 24, and the twins were born by breech extraction at 32 weeks' gestation. They were female and their combined weight was 3·17 kg. They were joined face-to-face from about the third rib to the umbilicus.

On examination there was a single umbilical cord in the midline. They were both cyanosed and acidaemic. There was no evidence of cardiac failure and the peripheral pulses were considered to be normal. Electrocardiogram showed synchronous electrical activity.

They underwent cardiac catheterisation and angiography on the day of admission. Because of the poor condition of the twins full data were not obtained, though it was clear that there was free communication between the two hearts at atrial level, and in both there was total anomalous pulmonary venous drainage. Operation was considered impossible and the twins died soon after cardiac catheterisation was completed.

Necropsy showed the following.

TWIN A

There was tricuspid and pulmonary atresia as well as total anomalous venous drainage to the coronary sinus. The right atrium communicated with the left atrium via a patent foramen ovale. There was a small partially closed ductus arteriosus which communicated directly with small pulmonary arteries.

TWIN B

Again there was total anomalous pulmonary venous drainage to the coronary sinus. In addition there was aortic atresia and a very small left ventricle (hypoplastic left heart syndrome). The mitral and tricuspid valves were normal. There was a communication between the left and right atria via a patent foramen ovale. The pulmonary arteries appeared normal and there was a huge ductus arteriosus.

There was free communication between the two hearts, from the right atria of Twin A to the coronary sinus of Twin B.

There was also a large fused liver. The gastrointestinal system was otherwise normal.

Case 3

The conjoined twins, both female, were admitted to The Hospital for Sick Children, in May 1969, aged 24 hours. They were born at 39 weeks' gestation by caesarian section. Their combined weight was 5·2 kg. Their mother was 30 years of age and had had two previous miscarriages. The twins were joined from about 2 cm below the suprasternal notch downwards to the upper edge of the common omphalocele.

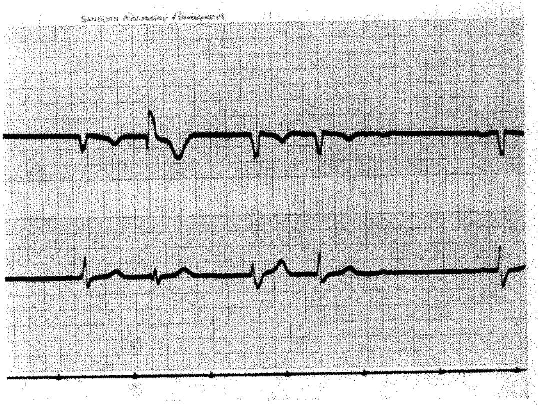

Fig. 1 *Bipolar lead II electrocardiogram in case 3. Upper tracing (Twin A), lower tracing (Twin B) show identical ventricular rate. Ventricular extrasystole (beat 2) in both tracings. Sinus capture (last beat).*

On admission their general condition was good and they were acyanotic. The peripheral pulses were all easily felt and there was no clinical evidence of congestive heart failure. The electrocardiogram showed nodal rhythm, and there was evidence of two electrically independent hearts (Fig. 1).

Cardiac catheterisation on the day of admission showed the following.

TWIN A
There was a single atrium and the two ventricles were connected by a ventricular septal defect. An inferior ventricle gave rise to an anterior aorta and an anterosuperior ventricle gave rise to a posterior pulmonary artery. The aorta and pulmonary artery appeared normal.

TWIN B
There was a single atrium and a single ventricle. The pulmonary artery and aorta appeared normal and were normally related. There was a ductus arteriosus with a shunt from pulmonary artery to aorta on angiography.

The two hearts communicated at atrial and ventricular levels.

These findings rendered surgical intervention impossible, but oral feeding was started. On the fourth day of life the twins became cyanosed with a gradual increase in respiratory rate and eventually died later that day.

Necropsy showed distortion of the thoracic cage with a cleft-like space on the right which had considerably reduced the space available for pulmonary development so that both lungs had a pronounced degree of hypoplasia. There was a single large fused heart shared by the twins, and the cardiac lesions were those described at catheterisation. There were thus three ventricles with one common chamber.

The bowel of both twins was normal. The liver of each twin was fused in the mid-line to form one very large organ weighing 150 g; separate gall-bladders and bile ducts were present and the pancreas in both cases was normal. No other abnormalities were detected.

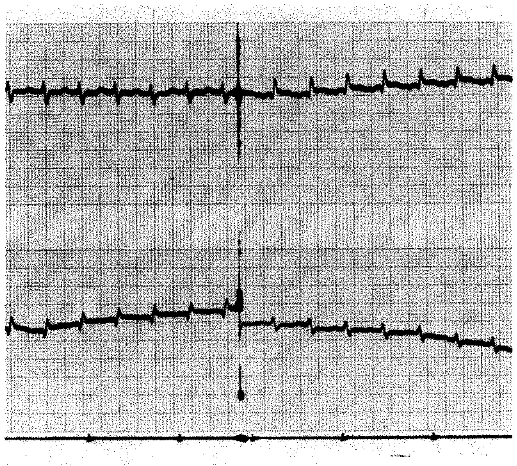

Fig. 2 *Bipolar leads aVL and aVF in case 4. Upper trace (Twin A), lower trace (Twin B) show identical rates.*

Case 4

The twins, both female, were born after an elective lower segment caesarian section. The pregnancy had been uneventful, and the parents already had one normal child. Simultaneous electrocardiograms (Fig. 2) showed identical heart rates, and the twins were transferred to The Hospital for Sick Children, in May 1976. The combined weight of the twins was 4·8 kg. The twins were joined from the lower one-third of the sternum down to the umbilicus. There was a small omphalocele at the lower part of the junction. The external features of the upper and lower parts were normal. All peripheral pulses were felt and both twins were tachypnoeic. Twin B was moderately cyanosed.

At cardiac catheterisation, the following abnormalities were found.

TWIN A
A distinctly separate inferior vena cava led to the right atrium. A ventricle (morphological left ventricle) was entered from the right atrium. The ventricle lay horizontally across the thorax of Twin B (Fig. 3). The ventriculogram showed a primitive ventricle with an outlet chamber. Both the great arteries seemed to arise from the main chamber (Fig. 3a and 3b), the aorta being superiorly placed. Right atrial angiogram also opacified the inferior vena cava of Twin B.

TWIN B
There was a large communication between the two atria. A ventricle was entered from the left atrium. A ventriculogram confirmed primitive ventricle with obvious subpulmonary stenosis.

Left atrial injection showed the presence of a common atrium (Fig. 4). Oxygen saturations in Twin A and B suggested that the respective ventricles were separate.

It was decided to separate the twins, though the exact site of atrial communication was not known. At operation there was a common pericardial sac. There was communication between the right atrium

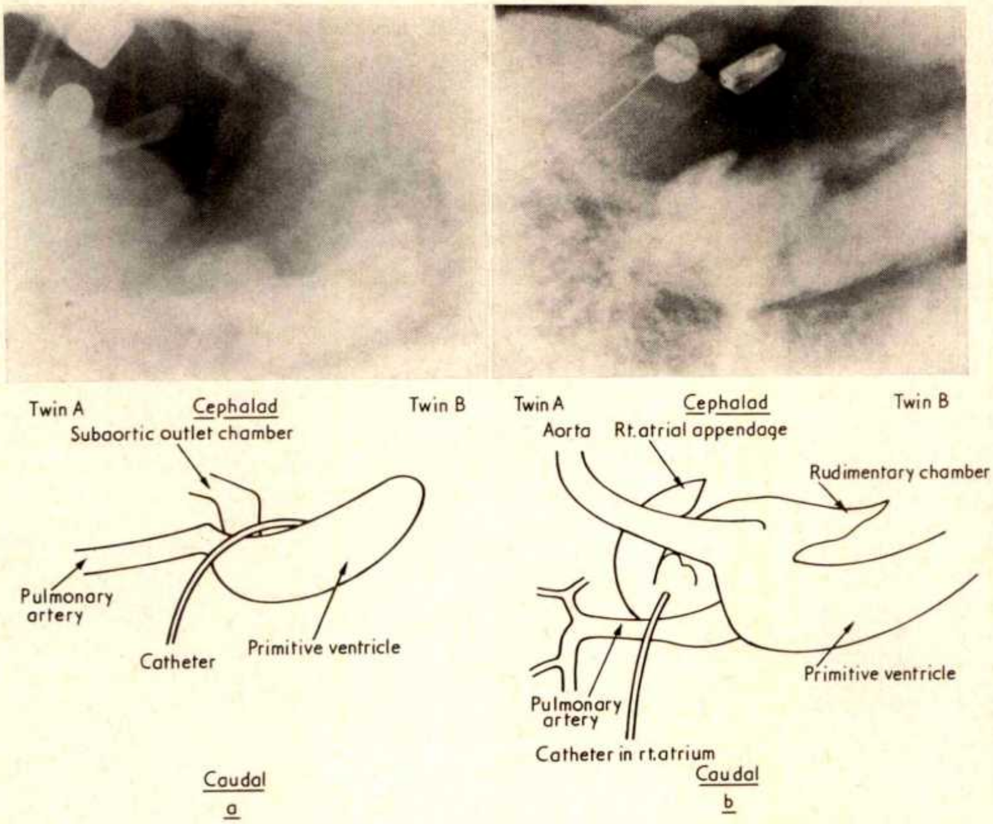

Fig. 3 *(a) Angiocardiogram in ventricle of Twin A and (b) line drawing of (a) show primitive ventricle with rudimentary outlet chamber (superior). Aorta is superior to pulmonary artery.*

of twin B and the coronary sinus of twin A. Separation of the cardiovascular communication was achieved. The liver was divided and in twin A duodeno-ileal anastomosis was performed. Twin B died towards the end of the procedure and twin A died 14 hours later.

Necropsy showed a primitive ventricle with transposition of the great arteries in twin A. There were two atrioventricular valves leading to the common ventricle. Twin B had tricuspid atresia and pulmonary stenosis with a rudimentary right ventricle. The large left ventricle gave rise to the aorta and the pulmonary arteries were supplied by a ductus arteriosus. There was also a common atrium. The mitral valve was normal.

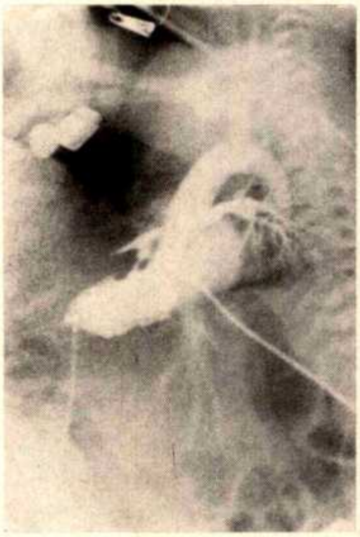

Fig. 4 *Angiocardiogram of left atrium (Twin B) shows opacification of inferior vena cava. There is a primitive ventricle, a superior rudimentary outlet chamber, and pulmonary stenosis.*

Discussion

The nature of the cardiovascular anomalies in our series of thoracopagus twins has been summarised

Table *Cardiovascular abnormalities in thoracopagus conjoined twins*

Case No.	*Twin A*	*Twin B*	*Site of intracardiac union*
1	Hypoplastic left ventricle; mitral atresia; bicuspid aortic valve	Primitive ventricle (subaortic outlet chamber)	Ventricular
2	Tricuspid and pulmonary atresia; total anomalous pulmonary venous drainage; hypoplastic right ventricle	Aortic atresia; hypoplastic left ventricle; total anomalous pulmonary venous drainage	Right atrium (Twin A) to coronary sinus (Twin B)
3	Common atrium; large ventricular septal defect	Common atrium; common ventricle	Ventricular (common ventricle)
4	Primitive ventricle (anterior aortic origin)	Tricuspid atresia; severe pulmonary stenosis; hypoplastic right ventricle	Right atrium (Twin B) to coronary sinus (Twin A)

in the Table. The most common abnormality was some form of univentricular heart. The communication between the two hearts was at ventricular level in cases 1 and 3. Hence only cases 2 and 4 were potentially suitable for separation. However, the severe cardiovascular anomalies in the individual hearts would have required palliative procedures as well.

Cardiovascular anomalies were described in 45 sets of twins by Nichols *et al.* (1967) who found that 75 per cent of thoracopagus twins had common hearts and in 90 per cent there was a common pericardial sac. The cardiac malformations in their series were as follows: 2 separate ventricles (10 cases); 3 ventricles (12 cases); 2 ventricles (1 for each twin) (19 cases); and 1 ventricle for both (4 cases).

Specific cardiac malformations included pulmonary atresia and absence of ventricular septum. The cardiovascular abnormalities in our own cases are in accord with those described in this series.

The importance of preoperative cardiac evaluation has been emphasised by Simpson *et al.* (1970). Electrocardiographic examination in the twins seems to be a reliable guide as to whether the hearts are fused; identical heart rates were recorded in all our 4 cases and there was invariably a major communication between the hearts of the twins (Fig. 1 and 2).

Full cardiac catheterisation with selective angiocardiograms is essential before separation is considered. The exact timing of the separation is often difficult, but in our series all the twins were extremely ill and required urgent investigations. Even after successful separation, the presence of severe cardiovascular lesions may make survival unlikely without further palliative surgical procedures for each twin.

We are grateful to our surgical colleagues—Mr. D. Eckstein (case 4), Mr. D. Waterston (case 1), and Professor J. Wilkinson (case 3) under whose care the patients were admitted. Mr. J. Stark, Mr. M. de Leval, and Mr. Eckstein performed the separation in case 4.

References

Amiel, G. J. (1967). Conjoined entire twins. *British Journal of Clinical Practice,* **21,** 141–146.

Leachman, R. D., Larson, J. R., Kohler, C. M., and McNamara, D. G. (1967). Cardiovascular evaluation of conjoined twins. In *Conjoined Twin's Birth Defects. Original Article series* 3 (No. 1), pp. 56–62. Ed. by Daniel Bergsma. National Foundation, New York.

Morrison, J. E. (1963). *Foetal and Neonatal Pathology,* 2nd ed. Butterworths, London.

Mulcare, R. J., Bhokakul, P., Potitung, P., and Wheeler, B. (1970). The surgical separation of the thoracopagus conjoined twins of Korat, Thailand. *Annals of Surgery,* **172,** 91–97.

Nichols, B. L., Blattner, R. J., and Rudolph, A. J. (1967). General clinical management of thoracopagus twins. In *Conjoined Twins, Birth Defects. Original Article series 3* (No. 1), p. 38. Ed. by Daniel Bergsma. National Foundation, New York.

Simpson, J. S., Mustard, W. T., Moes, C. A. F., and Izukawa, T. (1970). Emergency separation of thoracopagus (twins cojoined at thorax) in the newborn period: importance of careful pre-operative cardiac evaluation. *Surgery,* **67,** 697–702.

Tandon, R., Sterns, L. P., and Edwards, J. E. (1974). Thoracopagus twins. *Archives of Pathology,* **98,** 248–251.

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Effect of additional valve lesions on left ventricular ejection time in aortic stenosis

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Rate-corrected left ventricular ejection time was measured from the aortic pressure tracings of 171 catheterised patients with aortic valve area $\leq 1{\cdot}2$ cm^2. In 50 patients with pure aortic stenosis, left ventricular ejection time increased with decreasing valve area and was significantly higher (468±5 ms, mean±SEM) than in 13 normal subjects (435±5 ms). Additional aortic regurgitation in 72 patients further increased the left ventricular ejection time to 484±4 ms.

Significant mitral stenosis (mitral valve area $\leq 1{\cdot}2$ cm^2) in 6 patients with aortic stenosis and 33 patients with aortic stenosis and regurgitation reduced the left ventricular ejection time to normal. Similarly, severe mitral regurgitation in 3 patients with aortic stenosis and regurgitation reduced left ventricular ejection time to normal, though slight or moderate mitral regurgitation in 7 of these patients did not.

These data show that the prolonged left ventricular ejection time in aortic valve disease may be restored to normal in the presence of coexisting significant mitral disease.

Prolongation of the rate-corrected left ventricular ejection time is associated with significant aortic stenosis or aortic regurgitation (Katz and Feil, 1925; Benchimol *et al.*, 1960; Parisi *et al.*, 1971; Bonner *et al.*, 1973; Bache *et al.*, 1973). Though depressed left ventricular function of ischaemic or myopathic aetiology generally shortens the left ventricular ejection time (Weissler *et al.*, 1961; Weissler *et al.*, 1968, 1969; Heikkilä *et al.*, 1971; Pouget *et al.*, 1971; McConahay *et al.*, 1972), it has recently been shown that congestive failure secondary to aortic stenosis can be distinguished from these by persistence of prolongation of left ventricular ejection time (Bonner and Tavel, 1973). Though it is widely appreciated in clinical practice that mitral valvular disease may alter the pulse contour expected in aortic disease, no quantitative study to emphasise and document this effect is available other than the partial data presented by Epstein and Coulshed (1964). Since additional valve lesions commonly exist in the presence of important aortic stenosis, and since mitral valve lesions may be associated with left ventricular ejection time shortening (Benchimol *et al.*, 1960; Moskowitz and Wechsler, 1965; Elkins *et al.*, 1967; Tavel *et al.*, 1972), the present study was designed to quantify the effect of additional lesions on the prolonged left ventricular ejection time of aortic stenosis.

Methods

Left ventricular ejection time was measured from the central aortic pulse tracing obtained at cardiac catheterisation in 171 patients with calculated aortic valve areas of 1·2 cm^2 or less, with clear identification of onset of ejection and incisura. Left ventricular ejection time in ms was measured from the onset of ejection to the incisura and an average value was determined for 4 cycles. Rate correction was performed according to the regression data of Weissler *et al.* (1969) for patients in sinus rhythm; for men, left ventricular ejection time = measured ejection time + 1·7 × heart rate. For patients with atrial fibrillation, an average value was calculated for cycles of similar length and the average heart rate of these cycles was used for rate correction.

Of the 171 patients, 50 had pure aortic stenosis with valve areas calculated from the Gorlin formula (Gorlin and Gorlin, 1951) (constant = 44·5) from 0·3 cm^2 to 1·2 cm^2. Rate corrected left ventricular ejection time was compared with calculated orifice size. Mean values of left ventricular ejection time

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for valve areas between 0·3 cm² and 0·8 cm² ('severe' aortic stenosis), between 0·9 cm² and 1·2 cm² ('moderately severe' aortic stenosis), and for the total group were calculated.

Seventy-two patients had varying degrees of additional aortic regurgitation. This was classified as slight if the aortic root injection disclosed regurgitation of contrast that was cleared from the left ventricle during several beats. Moderate regurgitation was defined as progressive opacification of the ventricle following root injection. Severe regurgitation was defined as ventricular opacification during the one or two beats after root injection. Mean left ventricular ejection time values were calculated for the total aortic stenosis and regurgitation group and also for subgroups arranged according to the degree of aortic stenosis and the amount of aortic regurgitation.

Additional mitral stenosis, with valve areas less than 1·2 cm² calculated from the Gorlin formula, was found in 3 patients with pure aortic stenosis and 12 patients with combined aortic stenosis and regurgitation. Three patients with aortic stenosis and mitral stenosis had additional slight or moderate mitral regurgitation, and 21 patients with aortic stenosis and regurgitation and mitral stenosis had additional slight mitral regurgitation.

Slight mitral regurgitation was defined as regurgitation of contrast on left ventricular injection that failed to opacify the left atrium. Moderate mitral regurgitation was defined as progressive opacification of the atrium, and severe mitral regurgitation as opacification of the atrium over one or two beats. Seven patients had slight or moderate mitral regurgitation in addition to aortic stenosis and regurgitation. Only 3 patients had severe mitral regurgitation in addition to aortic stenosis and regurgitation, and these had additional slight mitral stenosis, with valve areas greater than 1·2 cm². There were no patients with significant aortic stenosis and additional pure severe mitral regurgitation.

For comparison, mean left ventricular ejection time was calculated for 13 subjects with normal values and ventricular function, 19 patients with pure isolated mitral stenosis, and 9 patients with pure mitral regurgitation.

Results

Patient grouping and results are outlined in the Table.

NORMAL PATIENTS

Mean left ventricular ejection time ±SEM for 13 normal subjects was 435 ±5 ms.

Table

Group	*No. of patients*	*LVET (ms ± SEM)*
Normal	13	435 ±5
Aortic stenosis alone		
Aortic stenosis: total	50	468 ±5
Moderately severe aortic stenosis (0·9–1·2)	13	447 ±6
Severe aortic stenosis (≤0·8)	37	474 ±6
Additional aortic regurgitation		
Aortic stenosis and regurgitation total:	72	484 ±4
Aortic regurgitation: slight	35	478 ±6
Moderately severe aortic stenosis	8	459 ±15
Severe aortic stenosis	27	483 ±6
Aortic regurgitation: moderate	27	493 ±6
Moderately severe aortic stenosis	7	476 ±12
Severe aortic stenosis	20	499 ±9
Aortic regurgitation: severe	10	485 ±14
Moderately severe aortic stenosis	5	486 ±24
Severe aortic stenosis	5	484 ±16
Additional mitral stenosis		
Aortic stenosis and mitral stenosis	3	428 ±8
Aortic and mitral stenosis, slight, moderate mitral regurgitation	3	425 ±11
Aortic stenosis and regurgitation, and mitral stenosis	12	435 ±7
Aortic stenosis and regurgitation and mitral stenosis, slight mitral regurgitation	21	437 ±10
Pure mitral stenosis	19	409 ±11
Additional mitral regurgitation		
Aortic stenosis and regurgitation, slight, moderate regurgitation	7	481 ±8
Aortic stenosis and regurgitation, severe mitral regurgitation, slight mitral stenosis	3	432 ±19
Pure severe mitral regurgitation	9	383 ±10

AORTIC STENOSIS

In the group of patients with pure aortic stenosis, left ventricular ejection time tended to increase with decreasing valve area, as seen in Fig. 1. Regression data relating the variables, left ventricular

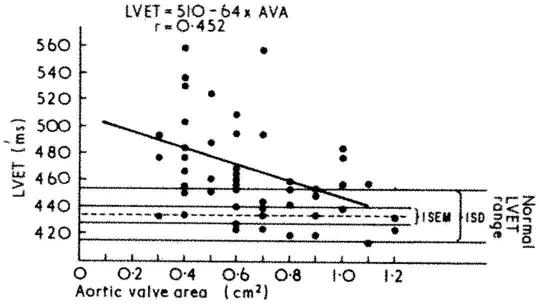

Fig. 1 *Left ventricular ejection time (LVET) in 50 patients with calculated aortic valve between 0·3 and 1·2 cm², showing increasing left ventricular ejection time with decreasing orifice size. Linear correlation is poor, and considerable overlap with normal exists for valve areas >0·6 cm².*

ejection time = −64 aortic valve area + 510, showed wide scatter ($r = -0{\cdot}45$). Patients with moderately severe aortic stenosis (valve area 0·9–1·2 cm^2) had a mean left ventricular ejection time of 447 ± 6 ms, higher than mean normal, but not significantly ($P < 0{\cdot}10$). Patients with severe aortic stenosis (valve area ≤0·8 cm^2) had a mean left ventricular ejection time of 474 ± 6 ms, significantly higher than both the normal group and less severe aortic stenosis subgroup ($P < 0{\cdot}001$). The mean left ventricular ejection time for the entire aortic stenosis group of 468 ± 5 ms was significantly higher than normal ($P < 0{\cdot}005$) (Fig. 2).

ADDITIONAL AORTIC REGURGITATION

The effect of varying degrees of aortic regurgitation on the left ventricular ejection time in 72 patients with aortic stenosis is shown in Fig. 3. For any calculated valve area, additional aortic regurgitation further increased the left ventricular ejection time. With slight aortic regurgitation, left ventricular ejection time for patients with aortic valve areas ≤1·2 cm^2 rose to 478 ± 6 ms ($P < 0{\cdot}05$). The increase with moderate aortic regurgitation was more pronounced, with a mean left ventricular ejection time of 493 ± 7 ms ($P < 0{\cdot}005$). With severe aortic regurgitation, the mean left ventricular ejection time of 485 ± 13 ms was not significantly higher than the pure aortic stenosis group ($P < 0{\cdot}10$), and was slightly lower than the moderate aortic regurgitation subgroup. For all patients with aortic regurgitation in addition to aortic stenosis, the left ventricular ejection time of 484 ± 4 ms was significantly greater than both the normal ($P < 0{\cdot}001$) and pure aortic stenosis ($P < 0{\cdot}01$) groups.

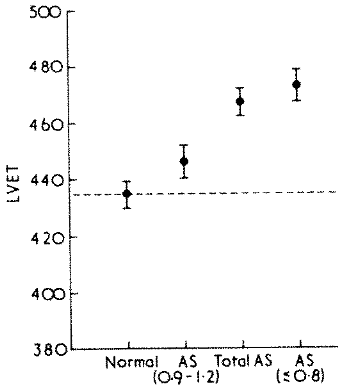

Fig. 2 *Mean left ventricular ejection time (LVET) ± SEM for subgroups of patients with varying severity of pure aortic stenosis (AS). The mean value for the total group is significantly higher than normal.*

ADDITIONAL MITRAL STENOSIS

The effect of mitral stenosis on the prolongation of left ventricular ejection time in aortic valve disease is shown in Fig. 4. In 19 patients with pure mitral stenosis (valve area < 1·2 cm^2) and no aortic disease, the left ventricular ejection time of 409 ± 17 ms was significantly lower than the normal, pure aortic stenosis, and aortic stenosis and regurgitation group means ($P < 0{\cdot}001$). With additional important

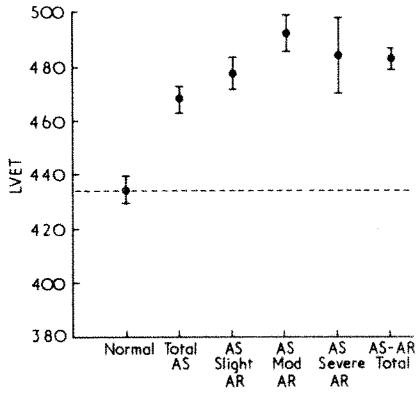

Fig. 3 *Effect of varying additional degrees of aortic regurgitation (AR) on the left ventricular ejection time in aortic stenosis (AS). The mean value for the total aortic stenosis-aortic regurgitation (AS-AR) group is significantly higher than both the normal and total aortic stenosis groups.*

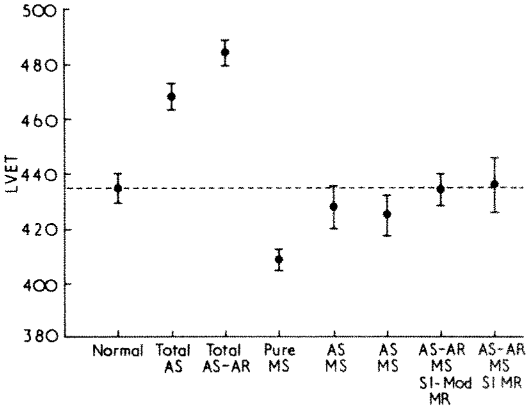

Fig. 4 *Effect of additional significant mitral stenosis (MS) on the left ventricular ejection time (LVET). Normalisation of left ventricular ejection time results when mitral stenosis coincides with aortic stenosis (AS) or with combined aortc stenosis and regurgitation (AS-AR). Sl = slight; Mod = moderate.*

mitral stenosis, the mean left ventricular ejection time in 3 patients with aortic stenosis of 428 ± 8 ms was significantly lower than the left ventricular ejection time in the pure aortic stenosis group ($P < 0{\cdot}05$), and not significantly different from normal. In 3 patients with slight or moderate mitral regurgitation in addition to mitral stenosis and aortic stenosis, the mean left ventricular ejection time of 425 ± 11 ms was no different from the mitral stenosis and aortic stenosis group and again not different from normal. Similarly, in 12 patients with aortic stenosis and regurgitation additional important mitral stenosis lowered the mean left ventricular ejection time to 435 ± 7 ms, a value significantly different from the pure aortic stenosis and mitral regurgitation group ($P < 0{\cdot}001$) and identical to normal. In 21 patients with slight mitral regurgitation in addition to mitral stenosis, aortic stenosis, and regurgitation, the mean left ventricular ejection time of 437 ± 10 ms was not significantly different from the mean left ventricular ejection time value of the important lesions together or from normal.

ADDITIONAL MITRAL REGURGITATION

The effect of additional mitral regurgitation on left ventricular ejection time prolongation in aortic valve disease is shown in Fig. 5. In 9 patients with pure severe mitral regurgitation and no aortic valve disease, the mean left ventricular ejection time of 383 ± 10 ms was significantly lower than normal, pure aortic stenosis, and aortic stenosis and regurgitation group means ($P < 0{\cdot}001$). Additional slight or moderate mitral regurgitation in 7 patients with aortic stenosis and regurgitation insignificantly lowered the mean left ventricular ejection time to 481 ± 8 ms compared with the pure aortic stenosis and regurgitation group, and this value remained significantly higher than normal ($P < 0{\cdot}001$). In 3 patients with severe mitral regurgitation, however, who had additional slight mitral stenosis (valve area $> 1{\cdot}2\ \text{cm}^2$) and aortic stenosis and regurgitation, the mean left ventricular ejection time of 432 ± 10 ms was significantly lower than the pure aortic stenosis and regurgitation group ($P < 0{\cdot}01$) but not significantly different from normal.

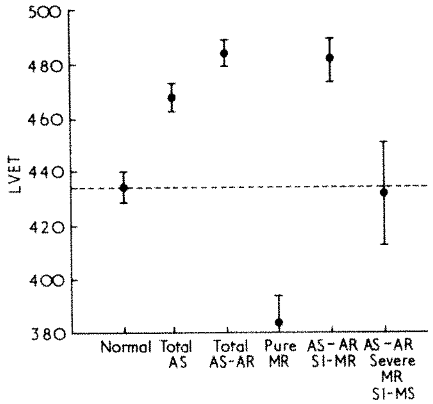

Fig. 5 *Effect of additional mitral regurgitation. Return to normal of left ventricular ejection time (LVET) results when severe mitral regurgitation (MR) coincides with aortic stenosis and regurgitation (AS-AR), but this effect is not seen with lesser degrees of mitral regurgitation (MR). Sl, slight.*

Discussion

The results of this study indicate that significant mitral stenosis and severe mitral regurgitation may return the left ventricular ejection time to normal in patients with aortic stenosis. Previous work has emphasised the clinical usefulness of left ventricular ejection time prolongation caused by outflow obstruction or high stroke volume in identifying patients with aortic stenosis or aortic regurgitation (Katz and Feil, 1925; Benchimol *et al.*, 1960; Parisi *et al.*, 1971; Bache *et al.*, 1973; Bonner *et al.*, 1973). It has also been shown that this prolongation is maintained in the presence of left ventricular failure caused by aortic stenosis (Bonner and Tavel, 1973), allowing separation of this important group to be made from patients with ventricular dysfunction of ischaemic, myopathic, and hypertensive aetiologies in which left ventricular ejection time is shortened (Weissler *et al.*, 1961; Weissler *et al.*, 1968, 1969; Heikkilä *et al.*, 1971; Pouget *et al.*, 1971; McConahay *et al.*, 1972).

Pure mitral stenosis is usually associated with a shortened left ventricular ejection time (Benchimol *et al.*, 1960; Moskowitz and Wechsler, 1965; Tavel *et al.*, 1972), depending in part on preceding cycle length for patients in atrial fibrillation (Kligfield, 1974), since left ventricular filling and subsequent ejection are limited by inflow obstruction and diastolic filling time. This was seen in our 19 patients with pure mitral stenosis.

In patients with both aortic and mitral lesions, our data confirm and extend the work of Epstein and Coulshed (1964), who showed progressive shortening of ejection time in aortic stenosis with increasing severity of mitral stenosis. However, the degree of aortic stenosis in their patients was not specified, and ejection times were corrected for heart rate by the Bazett formula rather than from regression data. In our patients, significant mitral stenosis reduced the left ventricular ejection time to normal in patients with aortic stenosis or combined aortic stenosis and regurgitation.

Pure severe mitral regurgitation is generally associated with a shortened left ventricular ejection time (Moskowitz and Wechsler, 1965; Elkins *et al.*, 1967), as seen in our 9 cases. With this lesion, abbreviation of ejection results from failure of the left ventricle to maintain forward flow during late systole (Elkins *et al.*, 1967). Other studies have reported normal duration of ejection in mitral regurgitation (Wiggers and Feil, 1921–1922; Nixon and Wagner, 1962), or were not rate corrected (Nixon and Wagner, 1962). It would be expected that lesser degrees of regurgitation would have less shortening effect on the left ventricular ejection time. This would account for the persistence of left ventricular ejection time prolongation in patients with aortic stenosis and regurgitation with only slight or moderate mitral regurgitation in this series compared with shortening to normal with additional severe regurgitation. In patients with combined aortic and mitral lesions (both mitral stenosis and regurgitation) the reduction of left ventricular ejection time to normal was not the result of left ventricular failure; there was no correlation between left ventricular ejection time and left ventricular end-diastolic pressure in patients with combined valvular lesions.

Use of the Gorlin formula tends to underestimate aortic valve area in the presence of aortic regurgitation, since calculated forward flow is less than the true cardiac output. Because of this, the degree of aortic stenosis in the patient groups with increasing regurgitation is correspondingly less than calculated. Milder stenosis may, therefore, account for the slight decrease in mean left ventricular ejection time in the aortic stenosis-severe aortic regurgitation group compared with the aortic stenosis-moderate regurgitation group. Alternatively, depressed ventricular function in the patients with severe aortic regurgitation may shorten the left ventricular ejection time, though there was no correlation between left ventricular end-diastolic pressure and left ventricular ejection time or between left ventricular end-diastolic pressure and aortic valve area in the 10 patients with aortic stenosis and severe aortic regurgitation. Whatever the mechanism, however, the difference from normal left ventricular ejection time at all levels of additional aortic regurgitation remains highly significant.

The effect of additional valve lesions on the duration of ejection in aortic stenosis therefore appears to be additive. Since mitral and aortic valve lesions frequently coexist, it is important to recognise that significant mitral disease can mask left ventricular ejection time prolongation, and conversely, that a normal left ventricular ejection time does not exclude severe mixed aortic and mitral disease. This is consistent with the well-recognised obscuring of physical signs that occurs in combined valvular disease (Katznelson *et al.*, 1960; Honey, 1961; Morrow *et al.*, 1962; Reid *et al.*, 1962; Zitnik *et al.*, 1965).

The duration of ejection measured from the central aortic pressure pulse has been shown to correlate closely with the left ventricular ejection time obtained non-invasively from external carotid pulse recording (Weissler *et al.*, 1961; Martin *et al.*, 1971). These results are, therefore, applicable to interpretation of standard systolic time intervals as popularised by Weissler *et al.* (1961, 1968). The regression data of Weissler *et al.* (1969) were used for rate correction in our patients, since these equations have become the standard for most investigators. Independently derived regression data for rate correction in our patients and in other series differ slightly from the equation used, but use of such data did not change the significance of the results presented. Though the direction of changes reported in this study is valid, each laboratory must establish its own range of normal before comparisons can be made.

It must also be appreciated that while valvular dysfunction affects the duration of ejection, independent variations of preload, contractile state, and afterload may alter left ventricular ejection time (Braunwald *et al.*, 1958; Weissler *et al.*, 1961; Heikkilä *et al.*, 1971; Martin *et al.*, 1971). This probably accounts for the wide range of values seen within each subgroup studied, so that even where mean values between groups are highly significantly different, some overlap of individual patient values generally occurs. This effect is well seen in the comparison of left ventricular ejection time and calculated valve area for patients with pure aortic stenosis. Only at valve areas below 0·6 cm^2 do the majority of left ventricular ejection time values not overlap the normal range, even though the mean left ventricular ejection time associated with valve areas below 0·9 cm^2 is highly significantly different from normal.

The poor correlation ($r = 0{\cdot}45$) between left ventricular ejection time and calculated aortic valve orifice area is similar to that found by Bache *et al.* (1973), though these workers were able to improve prediction of valve area with prolongation of ejection above a value obtained from stroke volume regression data. In the past, accurate stroke volume determination generally required intravascular measurement, so this correlation was of limited clinical usefulness. As noninvasive determination of stroke volume improves, for instance using ultrasound or radionuclide imaging, addition of stroke volume regression equations to carotid pulse left ventricular ejection time measurements may greatly improve indirect estimation of aortic valve orifice area.

References

Bache, R. J., Wang, Y., and Greenfield, J. C., Jr. (1973). Left ventricular ejection time in valvular aortic stenosis. *Circulation*, **47**, 527–533.

Benchimol, A., Dimond, E. G., and Shen, Y. (1960). Ejection time in aortic stenosis and mitral stenosis: comparison between the direct and indirect arterial tracings, with special reference to pre- and postoperative findings. *American Journal of Cardiology*, **5**, 728–743.

Bonner, A. J., Sacks, H. N., and Tavel, M. E. (1973). Assessing the severity of aortic stenosis by phonocardiography and external carotid pulse recordings. *Circulation*, **48**, 247–252.

Bonner, A. J., and Tavel, M. E. (1973). Systolic time intervals: use in congestive heart failure due to aortic stenosis. *Archives of Internal Medicine*, **132**, 816–819.

Braunwald, E., Sarnoff, S. J., and Stainsby, W. N. (1958). Determinants of duration and mean rate of ventricular ejection. *Circulation Research*, **6**, 319–325.

Elkins, R. C., Morrow, A. G., Vasko, J. S., and Braunwald, E. (1967). The effects of mitral regurgitation on the pattern of instantaneous aortic blood flow: clinical and experimental observations. *Circulation*, **36**, 45–53.

Epstein, E. J., and Coulshed, N. (1964). Assessment of aortic stenosis from the external carotid pulse wave. *British Heart Journal*, **26**, 84–96.

Gorlin, R., and Gorlin, S. G. (1951). Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I. *American Heart Journal*, **41**, 1–29.

Heikkilä, J., Luomanmäki, K., and Pyörälä, K. (1971). Serial observations on left ventricular dysfunction in acute myocardial infarction. II: Systolic time intervals in power failure. *Circulation*, **44**, 343–354.

Honey, M. (1961). Clinical and haemodynamic observations on combined mitral and aortic stenosis. *British Heart Journal*, **23**, 545–555.

Katz, L. N., and Feil, H. S. (1925). Clinical observations on the dynamics of ventricular systole. III—Aortic stenosis and aortic insufficiency. *Heart*, **12**, 171–180.

Katznelson, G., Jreissaty, R. M., Levinson, G. E., Stein, S. W., and Abelmann, W. A. (1960). Combined aortic and mitral stenosis: a clinical and physiological study. *American Journal of Medicine*, **29**, 242–256.

Kligfield, P. (1974). Systolic time intervals in atrial fibrillation and mitral stenosis. *British Heart Journal*, **36**, 798–805.

McConahay, D. R., Martin, C. M., and Cheitlin, M. D. (1972). Resting and exercise systolic time intervals: correlations with ventricular performance in patients with coronary artery disease. *Circulation*, **45**, 592–601.

Martin, C. E., Shaver, J. A., Thompson, M. E., Reddy, P. S., and Leonard, J. J. (1971). Direct correlation of external systolic time intervals with internal indices of left ventricular function in man. *Circulation*, **44**, 419–431.

Morrow, A. G., Awe, W. C., and Braunwald, E. (1962). Combined mitral and aortic stenosis. *British Heart Journal*, **24**, 606–612.

Moskowitz, R. L., and Wechsler, B. M. (1965). Left ventricular ejection time in aortic and mitral valve disease. *American Journal of Cardiology*, **15**, 809–814.

Nixon, P. G. F., and Wagner, G. R. (1962). The duration of left ventricular systole in mitral incompetence. *British Heart Journal*, **24**, 464–468.

Parisi, A. F., Salzman, S. H., and Schechter, E. (1971). Systolic time intervals in severe aortic valve disease. *Circulation*, **44**, 539–547.

Pouget, J. M., Harris, W. S., Mayron, B. R., and Naughton, J. P. (1971). Abnormal responses of the systolic time intervals to exercise in patients with angina pectoris. *Circulation*, **43**, 289–298.

Reid, J. M., Stevenson, J. G., Barclay, R. S., and Welsh, T. M. (1962). Combined aortic and mitral stenosis. *British Heart Journal*, **24**, 509–515.

Tavel, M. E., Baugh, D. O., Feigenbaum, H., and Nasser, W. K. (1972). Left ventricular ejection time in atrial fibrillation. *Circulation*, **46**, 744–752.

Weissler, A. M., Harris, W. S., and Schoenfeld, C. D. (1968). Systolic time intervals in heart failure in man. *Circulation*, **37**, 149–159.

Weissler, A. M., Harris, W. S., and Schoenfeld, C. D. (1969). Bedside technics for the evaluation of ventricular function in man. *American Journal of Cardiology*, **23**, 577–583.

Weissler, A. M., Peeler, R. G., and Roehll, W. H. (1961). Relationships between left ventricular ejection time, stroke volume and heart rate in normal individuals and patients with cardiovascular disease. *American Heart Journal*, **62**, 367–378.

Wiggers, C. J., and Feil, H. (1921–1922). The cardiodynamics of mitral insufficiency. *Heart*, **9**, 149–174.

Zitnik, R. S., Piemme, T. E., Messer, R. J., Reed, D. P., Hayes, F. W., and Dexter, L. (1965). The masking of aortic stenosis by mitral stenosis. *American Heart Journal*, **69**, 22–30.

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Detector electrode introduced by mediastinoscopy for atrial triggered cardiac pacing

A follow-up study of electrode function in 82 patients

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An atrial detector electrode was introduced by mediastinoscopy in 82 patients requiring permanent cardiac pacing. There were no complications. An adequate P wave was recorded in 80 patients. During the following week, the P wave became ineffective in 5 patients; angina occurred in 2 and atrial arrhythmias in 2. Atrially triggered ventricular pacing was established in 73 patients and was followed in 71 patients for a period of 1 to 113 months. In 7 cases, it had to be terminated because of an ineffective or unstable P wave, in 6 cases because of atrial arrhythmias, and in 4 cases because of advanced age and recurrent infections.

The method is technically simple and places little stress on the patient.

When permanent cardiac pacing was introduced (Weirich *et al.*, 1957; Furman and Schwedel, 1959; Glenn *et al.*, 1959; Senning, 1959; Elmqvist and Senning, 1960) the aim was to prevent Adams-Stokes attacks and death in patients with complete heart block. Fixed rate cardiac pacing meant an enormous benefit to these patients. With technical progress, greater demands have been made on cardiac pacing in order to avoid potentially dangerous interference between pacemaker rhythm and spontaneous beats and to help patients live a normal life without feeling discomfort or incapacity. Atrial triggered cardiac pacing means for many patients the achievement of this aim. The method was described in animal experiments by Folkman and Watkins (1957), Stephenson *et al.* (1959), Battye and Wheale (1960), and Nathan *et al.* (1963). It was introduced in the clinic by Center *et al.* (1963), who used an atrial sensing electrode introduced by thoracotomy.

At the Karolinska hospital atrial triggered cardiac pacing was introduced by Carlens *et al.* (1965) and Lagergren *et al.* (1966a, b) by means of an atrial sensing electrode introduced by mediastinoscopy (Carlens, 1959). The present paper reports a follow-up of operative results, the primary and late effectiveness of this type of atrial sensing electrode, and the cause of terminating atrial triggered cardiac pacing in all patients treated in this hospital by this method since 1964.

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Method

In the first stage a transvenous cardiac electrode was implanted and connected to an external pulse generator. During the past few years the stability of sinus rhythm and the amplitude of the P wave have been tested at rest and during exercise by means of an oesophageal electrode before implanting the mediastinal atrial sensing electrode. Fig. 1 shows the position of the mediastinal atrial electrode and Fig. 2 shows the close relation between it and the oesophageal electrode. Fig. 3 shows the P waves simultaneously recorded from both electrodes and Fig. 4 the standard leads with the atrial triggered cardiac pacemaker. The electrode used for mediastinal implantation was the Siemens-Elema EMT 588, and implantation was performed under general anaesthesia. A small incision was made in the jugular fossa and the front of the trachea was dissected. Under visual control through the mediastinoscope the dissection was continued by a 3 mm thick closed end suction tube past the point of bifurcation of the trachea and behind the right branch of the pulmonary artery to reach the layer of the connective tissue between the posterior wall of the left atrium and the oesophagus. Attempts were made to make a narrow tunnel slightly to the left of the midline. Best results were usually achieved 4 to 5 cm below the carina level. When this region had been located the electrode tip was gently advanced and, with the aid of forceps, placed in the

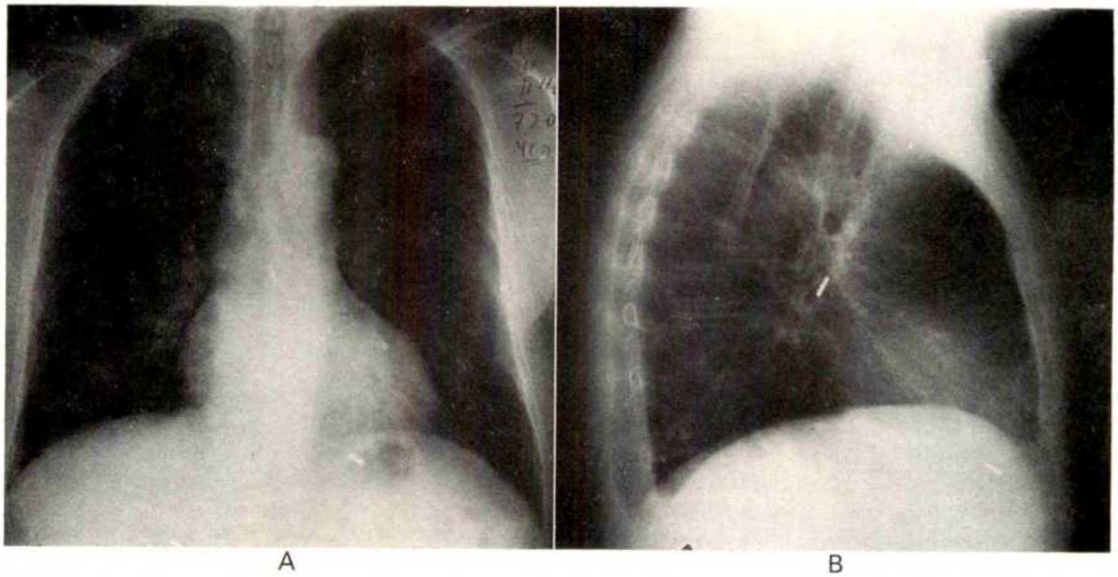

Fig. 1 X-*ray film in anteroposterior (A) and lateral (B) views visualising the mediastinal and the ventricular electrode in adequate position.*

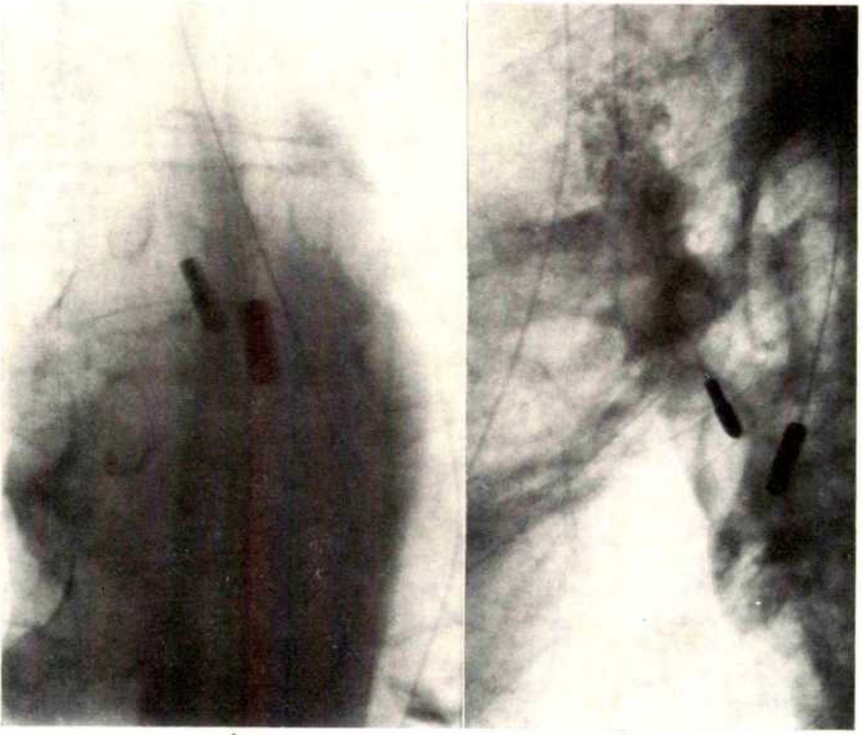

Fig. 2 X-*ray in antero (A) and lateral (B) views showing the close relation between the mediastinal and the oesophageal electrode. The upper electrode belongs to the mediastinal atrial electrode.*

connective tissue as close as possible to the atrial wall, while the amplitude of the P wave was checked on the electrocardiogram. Forcing the suction tube down involves the risk of both puncturing the pericardium and placing the electrode in an unstable position.

The amplitude from the positive to the negative deflection of the P wave was measured between the mediastinal atrial electrode and the right arm. The amplitude was not significantly different if the reference electrode was placed in the region of the generator pocket in the abdominal wall. More recently the positive and negative deflection of the P wave was measured separately because the input sensitivity of the pulse generator is more closely related to the positive and the negative deflections of the P wave rather than to the total amplitude. In order to get comparable values the total amplitude is given on the figures.

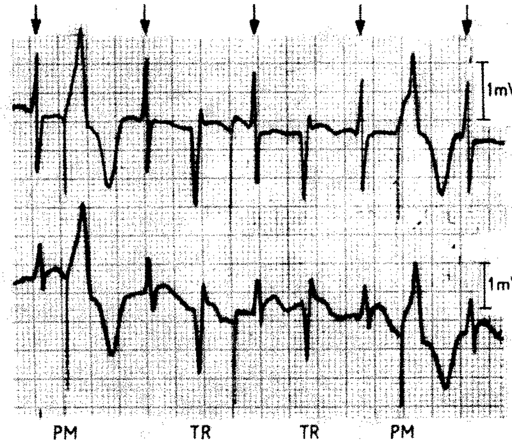

Fig. 3 *Electrocardiogram from mediastinal atrial electrode and oesophageal electrode.* Upper row, *recording between the right arm and the mediastinal electrode. The mediastinal atrial electrode is, thus, not connected to the atrial triggered pulse generator which is stimulating at its basic rate: 52 beats per min.* Lower row: *recording between the right arm and an oesophageal electrode. The recording was made at the same time as the* x-*ray film shown in Fig. 2. P waves are indicated by arrows and resemble each other in the two leads. There are both transmitted QRS complexes (TR) and pacemaker induced QRS complexes (PM). The second pacer artefact arrives in the refractory period. Paper speed: 25 mm per second.*

During the first period of this study a Siemens-Elema EM 141 pulse generator was used, requiring a P wave amplitude of at least 0·9 mV. Later on the more sensitive pulse generator, Siemens-Elema EM 144, EM 156/50, was constructed, which was triggered by a P wave of 0·5 to 0·4 mV.

When the P wave reached a stable value of at least 1 to 1·5 mV a loop was made in the neck and the electrode cable was drawn stepwise subcutaneously by means of a long injection needle, over the chest and abdomen to the left groin. The long subcutaneous tunnel minimised the risk of infection. The procedure, which has undergone only minor variations since it was first introduced, places very little strain on the patient.

If a second intervention for correction of the electrode placement was undertaken, varying degrees of scar formation could be found anterior to the trachea. In such cases the soft tissue to the right of the trachea was dissected. At the level of the right main bronchus a narrow tunnel was then dissected by the suction tube to the left of the midline.

The amplitude of the P wave after the operation often decreased during the first week after implantation and was checked repeatedly during 10 days. Before the atrial triggered generator was implanted the patient was tested with an externally coupled atrial triggered pulse generator at rest and during exercise. The amplitude of the P wave was thereafter routinely measured when replacement of the pulse generator was made.

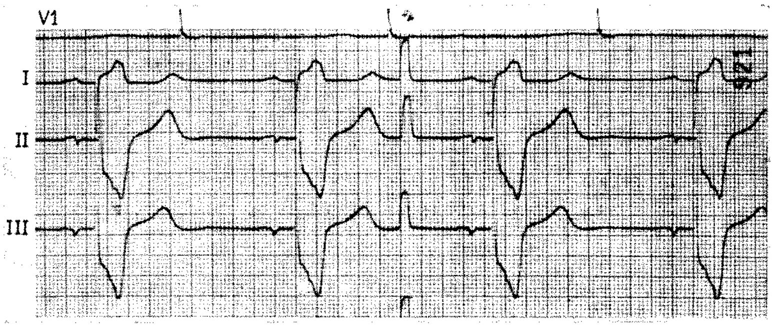

Fig. 4 *Electrocardiogram with atrial triggered cardiac pacing. Standard leads with the mediastinal electrode connected to the atrial triggered pulse generator in the same patient as in Fig. 1, 2, and 3. The small negative deflection of the P wave in leads II and III is caused by the P wave triggering the pulse generator. Paper speed: 50 mm per second.*

Table 1 *Review of case material*

No. of patients	*Age Mean ± SD (range)*	*No. starting atrial triggered cardiac pacing*	*Duration of atrial triggered cardiac pacing No. mean ± SD months (range)*	*No. terminating atrial triggered cardiac pacing*	*No. of deaths*	*No. of patients still undergoing atrial triggered cardiac pacing*
Men 44	55 ± 11 (26–70)	40	39* 39 ± 5 (1–103)	8	7	24
Women 38	52 ± 13 (29–69)	33	32* 46 ± 6 (4–113)	9	2	21

*1 patient lost from follow-up.

Subjects

The present study was based on 82 patients, 44 men and 38 women. The mean age was 55 years for men and 52 years for women (range 26 to 70 years) (Table 1). All patients in whom an attempt was made to introduce a mediastinal atrial pacing electrode in the period from 1964 to May 1974 were included in the study and all patients continuing to attend the Karolinska hospital for pulse generator replacements were included in the follow-up. In a few cases complementary information was obtained from hospitals outside the region of Stockholm.

In 9 patients atrial triggered cardiac pacing was not started (Table 2), and 2 patients with this type of pacing were lost from the follow-up.

The observation period in the remaining 71 patients ranged from 1 to 113 months. The mean observation period was 39 ± 5 SD months for men and 46 ± 6 SD months for women. During this control period 7 men and 2 women died. Death in 5 cases was not caused by pacemaker defect. In the remaining 4 cases the cause was unknown. In 17 cases (8 men and 9 women) atrial pacing had to be terminated. The reasons for this are discussed later. At the time of writing there are 45 cases (24 men and 21 women) still undergoing treatment.

Results

PRIMARY OPERATIVE RESULTS

An acceptable P wave with an amplitude of at least 1·0 to 1·5 mV was achieved in all patients except in the 2 cases reported below. The mean amplitude of the P wave at operation was 2·8 mV (range 1·3 to 5·0) in men and 2·5 mV (range 1·0 to 6·0) in women.

Table 2 *Different causes of not starting atrial triggered cardiac pacing*

Ineffective P wave preoperatively	*Ineffective P wave postoperatively*	*Anginal pains*	*Sinoatrial block*	*Atrial fibrillation*
2	3	2	1	1

A 38-year-old woman with congenital pulmonary and aortic stenosis showed normal P waves in standard leads. However, in the oesophageal lead the P wave was missing. An attempt was made to implant a mediastinal atrial pacing electrode but no suitable P wave could be obtained.

In a 68-year-old woman, operated on in 1964, the amplitude of the P wave from the mediastinal electrode was only 0·3 to 0·4 mV. No oesophageal lead was tried in this patient.

Postoperative *x*-ray control showed a displacement of the electrode into the pericardium in 2 patients but its position was easily adjusted: 1 of the 2 patients developed atrial fibrillation, which was converted, and when fibrillation subsequently recurred it was decided not to start atrial triggered cardiac pacing. In a third patient pleuropericarditis was observed 4 weeks after implantation; the exudate regressed spontaneously.

AMPLITUDE OF P WAVE

During the first week after the implantation of mediastinal atrial pacing electrode there was often a decrease of about 1 to 2 mV in the amplitude of the P wave (Fig. 5). In 2 of the 78 patients this decrease caused an inefficient P wave. In another 4 patients an inefficient P wave was caused by electrode displacement visualised by *x*-ray film (Table 3). Measurements of the P wave after starting atrial triggered cardiac pacing and during replacement of the generator showed moderate variations in amplitude, as shown in Fig. 6. After starting the pacing an inefficient P wave caused by electrode displacement occurred in 6 patients (Table 3). In 3 of them there had obviously been a very strong traction of the electrode by rotation of the pulse generator, during pregnancy or during replacement of a pulse generator. In the other cases the cause was obscure.

In one patient a broken electrode, which was easily repaired, caused an ineffective P wave.

CORRECTED AND RENEWED ELECTRODE IMPLANTATION

In 9 out of 13 patients with an inefficient P wave, attempts were made to correct or reimplant the mediastinal atrial electrode. In the other 4 patients already undergoing atrial triggered cardiac pacing this treatment was considered of less value for a variety of reasons, including advanced age. Out of the 4 cases in which an attempt was made to correct the mediastinal atrial electrode, one was successful one day after implantation and one successful one year after implantation. The two unsuccessful cases had displaced electrodes before starting atrial triggered cardiac pacing. Reimplantation functioned well in 4 out of 5 patients. In the fifth case, a 47-year-old woman, the second electrode became dislocated after 2 months. A third attempt was made but failed because of scar tissue in the mediastinum.

TERMINATED ATRIAL TRIGGERED CARDIAC PACING

Atrial triggered cardiac pacing was terminated in 17 cases for the various reasons shown in Table 4.

Table 4 *Different causes of termination of atrial triggered cardiac pacing*

Total No.	*Inefficient P wave*	*Unstable P wave*	*Sinus bradycardia or arrest*	*Atrial flutter or fibrillation*	*Other causes see text*
17	4	3	4	2	4

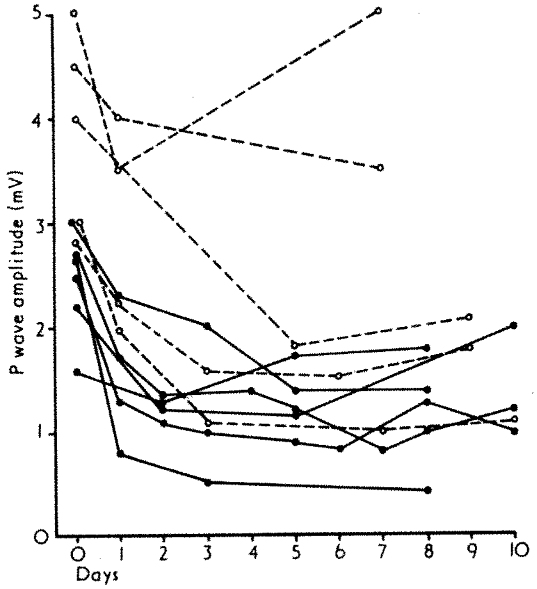

Fig. 5 *P wave amplitude in 11 cases illustrating the typical decrease of the amplitude during the first 10 days; men = ○, women = ●.*

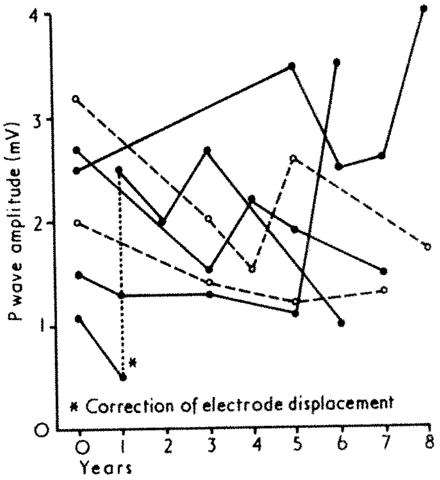

Fig. 6 *P wave amplitude in 6 cases illustrating the variation of the amplitude during treatment; men = ○, women = ●.*

Table 3 *Follow-up of primary P wave*

Acceptable at operation	*Inefficient before generator implant*	*Displacement before generator implant*	*Inefficient after starting atrial triggered cardiac pacing*	*Displacement after starting atrial triggered cardiac pacing*
No.	*No.*	*No.*	*No.*	*No.*
Men 44	3	2	4†	3
Women 36	4*	2	3	3
Total 80	7	4	7	6

*1 patient without *x*-ray control of the electrode position.

†1 patient with a broken cable.

The 4 cases (3 men and 1 woman) under the heading of 'other causes' include 2 of the men who developed other incapacitating illnesses during atrial triggered cardiac pacing.

The third man had developed atrioventricular block because of myocarditis, and during replacement of a pulse generator two years later it became apparent that the atrioventricular conduction was normal. He was, therefore, given ventricular triggered pacing in order to observe more easily if he could manage without cardiac pacing: this later proved to be the case.

In the case of the woman, recurrent perforations of the cable through the skin of the jugular fossa occurred, accompanied by a slight infection which did not heal until the mediastinal atrial electrode was removed.

In 3 patients, aged 70 to 80, atrial triggered cardiac pacing was temporarily interrupted and changed to ventricular synchronised pacing. In 2 cases this was done because of varying P waves, which were partly inefficient. All 3 patients, however, felt pronounced discomfort with breathlessness and decreased physical fitness, and the cardiac pacing was again changed to atrial triggered cardiac pacing. In case 3 a pulse generator with higher sensitivity to the P waves functioned well.

Discussion

With regard to the *capability of recording an adequate* P wave, the mediastinal atrial electrode has shown good results initially, with an effective P wave in 80 out of 82 cases. A *preoperative* screening of the mediastinal P wave should preferably be done by an oesophageal electrode to exclude patients with P waves unsuitable for a mediastinal atrial electrode.

The stability of the sinus rhythm should be checked by repeated electrocardiograms including one during exercise. An exercise test with increasing rate of the external pulse generator should also be done to eliminate patients who get anginal pains with increasing heart rate. Some of the early patients in this case material are not representative of patients selected for atrial triggered cardiac pacing more recently. In the early group it was started because of interference between fixed rate pacing and transmitted beats and because atrial triggered cardiac pacing was the first available method of synchronised pacing in this hospital. This explains why it was necessary to replace it with ventricular synchronised pacing in some of the early patients in this study.

The *surgical procedure* gave very little stress to the patients, and was free from complications with the exception of an easily corrected perforation of the electrode into the pericardium, which was seen in 2 patients. This might have been caused by excessive force on the suction tube.

The atrial fibrillation observed in one patient after implantation of mediastinal atrial electrode continued even after extraction of the electrode. It is possible, however, that the mechanical irritation may have provoked atrial fibrillation in a predisposed patient. The atrial fibrillation and flutter observed in 2 patients later on during atrial triggered cardiac pacing seems to be coincidental and an unpredictable cause of terminating it.

The regular decrease of the P wave after operation is most probably caused by tissue reaction against the electrode. During this period ineffectiveness of the P wave without visible displacement on *x*-ray film occurred only twice. The cause may have been extreme tissue reaction or minor displacement of the electrode. Visible displacement of the mediastinal atrial electrode with an ineffective P wave occurred in 10 patients up to 4 years after starting atrial triggered cardiac pacing. In some patients the cause was obviously an extreme traction of the mediastinal atrial electrode, as described above. After one week the P wave was usually stable during the years of observation. Several mediastinal atrial electrodes are still functioning after 10 years.

The mediastinal atrial electrode has previously been described as a promising method for atrial triggered cardiac pacing (Carlens *et al.*, 1965; Lagergren *et al.*, 1966a, b; Larsson *et al.*, 1969; Larsson, 1970; Kleinert and Nahrstedt, 1974). Larsson *et al.* (1969) presented results similar to this study, with no surgical complication and a displacement frequency of about 10 per cent.

The problem of displacement occurs with other types of electrodes, and our experience shows the importance of securing the electrode and of avoiding traction of it. For practical reasons and to reduce the risk of infection, Larsson *et al.* (1969) have suggested that it is preferable to do one stage implantation of the mediastinal atrial electrode and the atrial triggered pulse generator, even if early displacement of the electrode can still happen.

Apart from the mediastinal atrial electrode (Carlens *et al.*, 1965; Lagergren *et al.*, 1966a, b; Larsson *et al.*, 1969; Larsson, 1970; Kleinert and Nahrstedt, 1974) there are two main approaches for introducing the electrode: implantation via thoracotomy (Center *et al.*, 1963, 1964; Nathan *et al.*, 1964; Center and Nathan, 1966; Silverman *et al.*, 1968; Nusbaum and Levit, 1970; Cleveland *et al.*, 1972; Mills and Ochsner, 1973; Perryman and Sealy, 1973) and transvenous techniques (Rodewald *et al.*, 1964; Center and Castillo, 1967; Center *et al.*, 1967; Hunt and Sloman, 1968; Kastor *et al.*, 1969; Moss *et al.*, 1969; Kramer and Moss, 1970a, b; Kitamura *et al.*, 1971; Vogel *et al.*, 1971; Rosenkranz and Schaldach, 1971; Bleifeld *et al.*, 1971; Smyth *et al.*, 1971a, b; Porstmann *et al.*, 1972; Zucker *et al.*, 1973; Cappelen and Hall, 1974; Moss *et al.*, 1974; Obel and Scott Millar, 1975; Rubenfire, 1975). Reviews of different methods have been given by Dodinot *et al.* (1969), Sowton (1969), Benchimol and Goldstein (1969), Nathan *et al.* (1971), DeSanctis (1971), and Furman (1973).

The first method described and still most widely used is implantation *via thoracotomy*. With this method the electrode can be fixed directly on the atrium to ensure stability of the electrode. However, the method involves a relatively high risk, as stressed by Dodinot *et al.* (1969). In order to avoid such a major operation other surgical routes to the epicardium have been developed. The retrosternal approach through a subxiphoid incision (Behrends *et al.*, 1965; Bruck and Spang, 1966) seems to offer no significant advantages over thoracotomy.

The problem of the transvenous atrial electrode is the high frequency of electrode displacements (DeSanctis, 1971; Zucker *et al.*, 1973). However, Bleifeld *et al.* (1971), Rosenkranz and Schaldach (1971), and Vogel *et al.* (1971) have reported series of operations almost free from complications. Their methods involved using an electrode held tightly to the atrial wall by barbs or hooks on the electrode tip.

Among other transvenous methods, the J-shaped wires described and used by Kastor *et al.* (1969) and Smyth *et al.* (1971a, b) may be handled and inserted easily but the displacement frequency is high. Zucker *et al.* (1973) described a moderately successful modification of this method. Placing the transvenous electrode in the coronary vein (Hunt and Sloman, 1968; Moss *et al.*, 1969; Kramer and Moss, 1970a, b; Kitamura *et al.*, 1971; Moss *et al.*, 1974; Obel and Scott Millar, 1975; Rubenfire, 1975) has been used for long-term pacing. The potential risk of thrombosis and perforation must be considered but, as far as we know, only one case with perforation has been reported (Kitamura *et al.*, 1971): this occurred with a temporary electrode used in addition for infusion. The experience of this technique is still limited but promising results with low thresholds at generator replacements are reported by Moss *et al.* (1974).

In conclusion, the mediastinal atrial electrode has shown results that are comparable with the best results discussed above and the method has been shown to be suitable for long-term treatment.

The mediastinal atrial electrode has often been described as involving too high a risk and as being too difficult for general use, but our experience has shown that the method is technically simple and places little stress on the patient. It is, therefore, recommended as a good alternative for P wave detection.

References

Battye, C. K., and Weale, F. E. (1960). The use of the P-wave for control of a pacemaker in heart block. *Thorax*, **15**, 177–180.

Behrends, W., Bruck, A., Fürnrohr, H., and Mahringer, W. (1965). Implantation vorhofgesteuerter Schrittmacher ohne Thorakotomie an der Herzbasis. *Zeitschrift für Kreislaufforschung*, **54**, 934–936.

Benchimol, A., and Goldstein, M. (1969). A review of atrial pacing: clinical and laboratory applications. *Annals of the New York Academy of Sciences*, **167**, 604–613.

Bleifeld, W., Irnich, W., and Effert, S. (1971). A new transvenous electrode with myocardial fixation for permanent pacing. *Digest Ninth International Conference of Medical and Biological Engineering, Melbourne, Australia*, p. 76.

Bruck, A., and Spang, K. (1966). Der vorhofgesteuerte Schrittmacher. *Zeitschrift für Kreislaufforschung*, **55**, 282–297.

Cappelen, Chr., and Hall, K. V. (1974). Pervenous atrial electrode. *Scandinavian Journal of Thoracic and Cardiovascular Surgery*, **8**, 115–118.

Carlens, E. (1959). Mediastinoscopy: a method for inspection and tissue biopsy in the superior mediastinum. *Diseases of the Chest*, **36**, 343–352.

Carlens, E., Johansson, L., Karlöf, I., and Lagergren, H. (1965). New method for atrial-triggered pacemaker treatment without thoracotomy. *Journal of Thoracic and Cardiovascular Surgery*, **50**, 229–232.

Center, S., and Castillo, C. (1967). Pervenous synchronous pacing. *Journal of Thoracic and Cardiovascular Surgery*, **53**, 508–510.

Center, S., Castillo, C., and Keller, W. (1967). Permanent pervenous synchronous pacing of the heart. *Annals of Thoracic Surgery*, **4**, 218–231.

Center, S., and Nathan, D. (1966). The synchronous pacer. Three years of clinical experience with 45 cases. *Annals of Surgery*, **164**, 862–866.

Center, S., Nathan, D., Wu, C.-Y., and Duque, D. (1964). Two years of clinical experience with the synchronous pacer. *Journal of Thoracic and Cardiovascular Surgery*, **48**, 513–524.

Center, S., Nathan, D., Wu, C.-Y., Samet, P., and Keller, W. (1963). The implantable synchronous pacer in the treatment of complete heart block. *Journal of Thoracic and Cardiovascular Surgery*, **46**, 744–753.

Cleveland, R., Nelson, R., Zeilenga, D., and Lippmann, M. (1972). Atrial pacing following open-heart surgery. *Archives of Surgery*, **105**, 26–29.

DeSanctis, R. (1971). Diagnostic and therapeutic uses of atrial pacing. *Circulation*, **43**, 748–761.

Dodinot, B. P., Petitier, H. A., Gilgenkrantz, J. M., and Faivre, G. R. (1969). Clinical experience with atrial-synchronous pacing. *Annals of the New York Academy of Sciences*, **167**, 1038–1054.

Elmqvist, R., and Senning, Å. (1960). Implantable pacemaker for the heart. In *Medical Electronics, Proceedings of the 2nd International Conference*, p. 253. Ed. by C. N. Smyth. Charles C. Thomas, Springfield, Illinois.

Folkman, M. J., and Watkins, E. (1957). An artificial conduction system for the management of experimental complete heart block. *Surgical Forum*, **8**, 331–334.

Furman, S. (1973). Therapeutic uses of atrial pacing. *American Heart Journal*, **86,** 835–840.

Furman, S., and Schwedel, J. B. (1959). An intracardiac pacemaker for Stokes-Adams seizures. *New England Journal of Medicine,* **261,** 943–948.

Glenn, W. W. L., Mauro, A., Longo, E., Lavietes, P. H., and MacKay, F. J. (1959). Remote stimulation of the heart by radio-frequency transmission: clinical application to a patient with Stokes-Adams syndrome. *New England Journal of Medicine,* **261,** 948–951.

Hunt, D., and Sloman, G. (1968). Long-term electrode catheter pacing from coronary sinus. *British Medical Journal,* **4,** 495–496.

Kastor, J., DeSanctis, R., Leinbach, R., Harthorne, J. W., and Wolfson, I. N. (1969). Long-term pervenous atrial pacing. *Circulation,* **40,** 535–544.

Kitamura, K., Jorgensen, C. R., and From, A. H. L. (1971). Transvenous atrial and ventricular pacing from the coronary sinus complicated by perforation and cardiac tamponade. *Chest,* **60,** 95–98.

Kleinert, M., and Nahrstedt, J. (1974). Zur transmediastinalen Verlegung von Detektorelektroden bei vorhofgesteuerten elektrischen Stimulationssystemen. *Zeitschrift für Kardiologie,* **63,** 862–868.

Kramer, D. H., and Moss, A. (1970a). Permanent pervenous atrial pacing for treatment of symptomatic sinus bradycardia (abstract). *American Journal of Cardiology,* **25,** 111.

Kramer, D. H., and Moss, A. (1970b). Permanent pervenous atrial pacing from the coronary vein. *Circulation,* **42,** 427–436.

Lagergren, H., Johansson, L., Karlöf, I., and Thornander, H. (1966a). Atrial-triggered pacemaking without thoracotomy: apparatus and results in twenty cases. *Acta Chirurgica Scandinavica,* **132,** 678–695.

Lagergren, H., Johansson, L., Karlöf, I., and Thornander, H. (1966b). Ein neuer vorhofsgesteuerter Schrittmacher. *Thoraxchirurgie,* **14,** 594–597.

Larsson, S. (1970). Mediastinoscopy in pacemaker treatment. Mediastinoscopy. In *Proceedings of an International Symposium, Odense University.*

Larsson, S., Alestig, K., Bojs, G., and Bergh, N. P. (1969). Treatment by atrial-triggered pacemaker. *Scandinavian Journal of Thoracic and Cardiovascular Surgery,* **3,** 186–194.

Mills, N., and Ochsner, J. (1973). Experience with atrial pacemaker wires implanted during cardiac operations. *Journal of Thoracic and Cardiovascular Surgery,* **66,** 878–885.

Moss, A., Rivers, R., and Cooper, M. (1969). Long-term pervenous atrial pacing from the proximal portion of the coronary vein. *Journal of the American Medical Association,* **209,** 543–545.

Moss, A., Rivers, R., and Kramer, D. (1974). Permanent pervenous atrial pacing from the coronary vein. Long-term follow-up. *Circulation,* **49,** 222–225.

Nathan, D. A., Center, S., Samet, P., Wu, C.-Y., and Keller, J. W. (1964). The application of an unplantable synchronous pacer for the correction of Stokes-Adams attacks. *Annals of the New York Academy of Sciences,* **111,** 1093–1104.

Nathan, D. A., Center, S., Wu, C.-Y., and Keller, W. (1963). An implantable synchronous pacemaker for the long term correction of complete heart block. *American Journal of Cardiology,* **11,** 362–367.

Nathan, D., Lister, J., Castillo, R., Keller, W., and Gossellin, A. (1971). Current status of atrial pacing. *Annales de Cardiologie et d'Angéiologie,* **20,** 451–456.

Nusbaum, M., and Levit, S. (1970). Technique for permanent implantation of atrial pacemaker. *Surgery,* **68,** 916–918.

Obel, I. W. P., and Scott Millar, R. N. (1975). Long-term coronary sinus pacing. *Chest,* **67,** 741.

Perryman, R., and Sealy, W. (1973). Permanent atrial pacing. *Annals of Thoracic Surgery,* **15,** 16–24.

Porstmann, W., Witte, J., Dressler, L., Schaldach, M., Vogel, I., and Warnke, H. (1972). P-wave synchronous pacing using anchored atrial electrode implanted without thoracotomy. *American Journal of Cardiology,* **30,** 74–76.

Rodewald, G., Giebel, O., Harms, H., and Scheppokat, K. D. (1964). Intravenös-intrakardiale applikation von vorhofgesteuererten elektrischen Schrittmachern. *Zeitschrift für Kreislaufforschung,* **53,** 860–864.

Rosenkranz, K. A., and Schaldach, M. (1971). Transvenös-endokardiale vorhofsteuerung von Schrittmachern. *Deutsche medizinische Wochenschrift,* **96,** 680–686.

Rubenfire, M. (1975). Long-term coronary sinus pacing. *Chest,* **67,** 741.

Senning, Å. (1959). Discussion of paper by Stephenson, S. E., Jr., Edwards, W. H., Jolly, P. C., and Scott, H. W., Jr. Physiologic P-wave cardiac stimulator q.v. *Journal of Thoracic and Cardiovascular Surgery,* **38,** 639.

Silverman, L., Mankin, H., and McGoon, D. (1968). Surgical treatment of an inadequate sinus mechanism by implantation of a right atrial pacemaker electrode. *Journal of Thoracic and Cardiovascular Surgery,* **55,** 264–270.

Smyth, N., Keshishian, J., Bacos, J., Massumi, R., Fletcher, R., and Boivin, M. (1971a). Permanent pervenous atrial pacing. *Journal of Electrocardiology,* **4,** 299–306.

Smyth, N., Keshishian, J., Basu, A., Bacos, J., Massumi, R., Fletcher, R., and Baker, N. (1971b). Permanent transvenous atrial pacing: an experimental and clinical study. *Annals of Thoracic Surgery,* **11,** 360–370.

Sowton, E. (1969). Panel discussion II. *Annals of the New York Academy of Sciences,* **167,** 1067–1075.

Stephenson, S. E., Jr., Edwards, W. H., Jolly, P. C., and Scott, H. W., Jr. (1959). Physiologic P-wave cardiac stimulator. *Journal of Thoracic and Cardiovascular Surgery,* **38,** 604–609.

Vogel, I., Dressler, L., Witte, J., Warnke, H., Porstmann, P., and Schaldach, M. (1971). Atrial synchronized pacing using a new transvenous technique. *Annales de Cardiologie et d'Angéiologie,* **20,** 381–389.

Weirich, W. L., Gott, V. L., and Lillehei, C. W. (1957). The treatment of complete heart block by the combined use of a myocardial electrode and an artificial pacemaker. *Surgical Forum,* **8,** 360–363.

Zucker, R., Parsonnet, V., and Gilberg, L. (1973). A method of permanent transvenous implantation of an atrial electrode. *American Heart Journal,* **85,** 195–198.

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Alternans in human atrial monophasic action potential

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This report describes the case of a patient with a supraventricular tachycardia with a ventricular rate of 109/min and no visible P waves in the electrocardiogram. The recording of the monophasic action potential of the right atrium disclosed an atrial tachycardia with a rate of 218/min. There was an alternans of the phase 2 of repolarisation in the action potential. This report emphasises the fact that the phenomenon of alternans occurs in man, as in the experimental animal, at a cellular level.

Electrical alternation of the ventricular complexes in man was first reported by Lewis (1910). Reviews of further cases have been made by Hamburger *et al.* (1935), Spang (1957), Colvin (1958), Schamroth *et al.* (1959), Chung *et al.* (1964), and Bellet (1971). Alternation of the P waves has been described by Bernreiter (1956), Kisch (1949), and Piso (1956). To the best of our knowledge, alternation of the human atrial monophasic action potential has not been yet documented. Recently, we observed this phenomenon in one of our patients.

Case report

A 65-year-old man was admitted because of severe congestive heart failure. There was an earlier history of anterolateral myocardial infarction in 1965. During 1965 he also developed atrial fibrillation and was subsequently treated with digoxin 0·4 mg daily. Physical examination revealed signs of congestive heart failure. A grade 4/6 holosystolic murmur was present at the apex radiating to the axilla. The heart rhythm was regular, with a rate of 109/min. The blood pressure was 130/80 mmHg. There were moist râles at both bases. The liver was enlarged three finger breadths below the right costal margin.

Laboratory tests showed blood urea 14·9 mmol/l (89 mg/100 ml), creatinine 132·6 μmol/l (1·5 mg/100 ml), and digoxin 4·6 nmol/l (3·6 ng/ml). The other tests were within normal limits.

The electrocardiogram (Fig. 1) showed a regular supraventricular rhythm with no visible P waves. There were also significant Q waves in leads I, aVL, V5, and V6, compatible with an old anterolateral myocardial infarction.

In order to identify the atrial deflections, the right atrial monophasic action potential was recorded (Olsson *et al.*, 1971; Pop *et al.*, 1976). At this stage an atrial rate of 218/min, twice the ventricular rate (109/min), was seen (Fig. 2). The atrial deflections showed an alternans of the rate of repolarisation so that the duration of the monophasic action potential at 90 per cent of repolarisation alternately measured 170 and 210 ms, respectively.

In spite of intensive therapy, the patient's state deteriorated progressively and death occurred 3 days after admission. On the day before death, the patient again experienced atrial fibrillation.

Discussion

The patient had had persistent atrial fibrillation since 1965. Before admission he developed regular atrial tachycardia with a rate of 218/min and a 2:1 AV block associated with raised serum digoxin concentration. Thus the diagnosis of a digitalis-induced atrial tachycardia with block is easily made (Levine, 1966).

The monophasic action potential has a configuration similar to that of an action potential recorded in its immediate vicinity (Hoffman *et al.*, 1959). For this reason, the same notations are used for the depolarisation and for the repolarisation phases. Fig. 2 shows action potentials with distinct phase 2 of repolarisation. Such action potentials characterise the atrial specialised cells which have the potential to develop pacemaker activity (Hoffman and Cranefield, 1960; Hogan and Davis, 1968). The enhanced automaticity of such cells induced by digitalis presumably represents the electrophysiological basis of atrial tachycardia in our case (Hoffman and Singer, 1964). We assume that the group

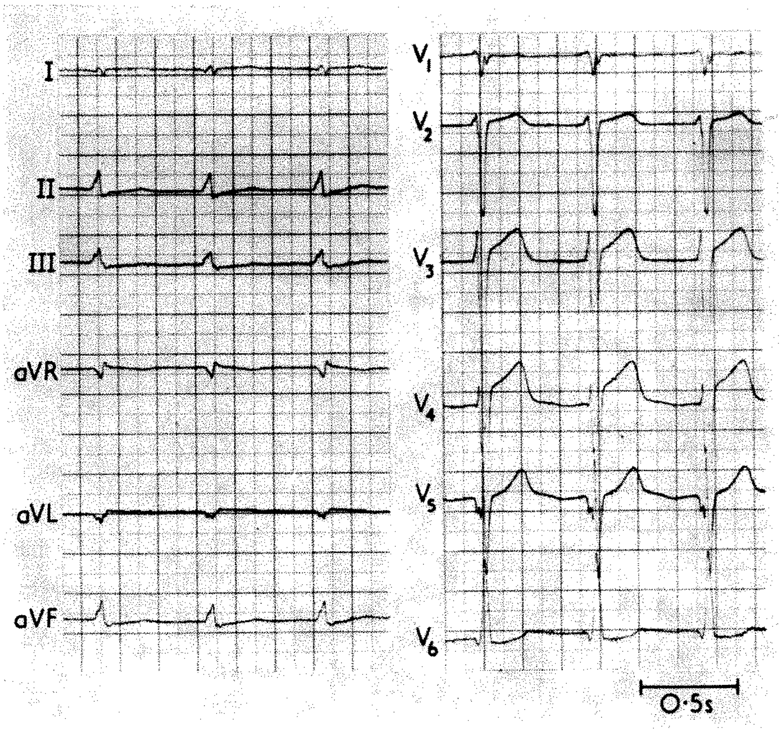

Fig. 1 *Electrocardiogram at admission (50 mm/s). No visible P waves. Regular ventricular rhythm with a rate of 109/min.*

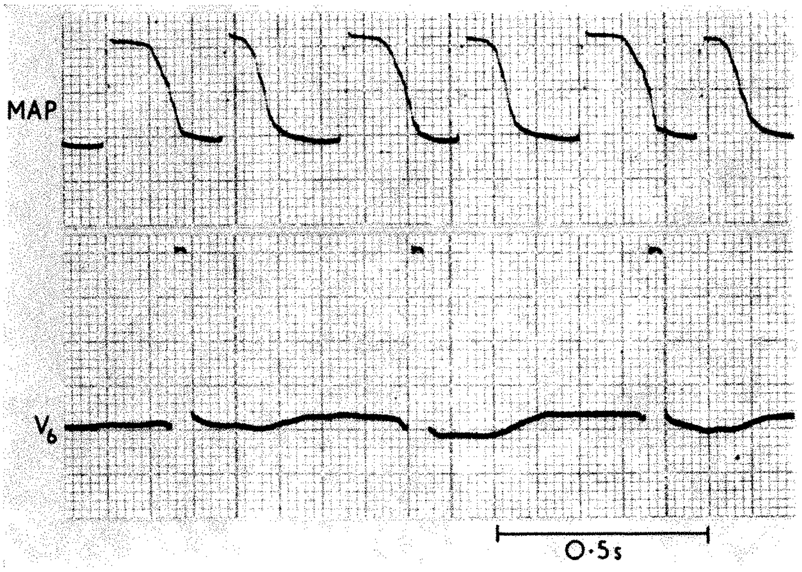

Fig. 2 *Top: monophasic action potential of the right atrium (MAP). Bottom: lead V6 recorded with threefold amplification. Alternans of phase 2 of repolarisation in the MAP.*

of cells from which the monophasic action potential was made do not represent the true pacemaker because the recording is devoid of slow diastolic depolarisation.

The first electrical alternans in the monophasic action potential in the experimental animal was described by Schütz as early as 1936. Using the technique for recording intracellular action potential (Ling and Gerard, 1949), the phenomenon of alternation was first described by Hoffman and

Suckling in 1954. By means of tri-iodothyronine, thyroxine, and acute anoxia, Kleinfeld *et al.* (1956) were able to reproduce, in single ventricular fibres of the frog heart, four types of electrical alternans; namely alternation in: (1) the rate of depolarisation, (2) the rate of repolarisation, (3) the magnitude of the action potential, and (4) hyperpolarisation.

In our case, there was an alternation of the rate of repolarisation; more precisely of phase 2 of repolarisation. As an explanation of the alternans observed in our patient, we propose the following hypothesis. During phase 2 of repolarisation, calcium and sodium ions flow across the membrane through the slow channel (Reuter, 1975; Zipes, 1976). The activation of this channel is not only voltage, but also time, dependent (Kohlhardt, 1975; Zipes, 1976). In our patient, during atrial tachycardia, the slow channel is fully opened only every second beat because of the fast rate. In this manner the phenomenon of alternans is to be seen as 2/1 alternation in the degree of opening of the slow channel.

The alternans of the monophasic action potential has not yet been seen in patients with atrial flutter, an arrhythmia with a higher rate than the atrial tachycardia (Olsson, 1971; Gavrilescu *et al.*, 1973). We assume, therefore, that in our case the alternans is not a physiological rate-dependent phenomenon, but merely the result of a disorder in the atrial cell membrane.

Three days after the recording of the monophasic action potential, the patient died. Whether the alternans of the atrial monophasic action potential is a sign of poor prognosis remains to be clarified by further investigations.

References

Bellet, S. (1971). *Clinical Disorders of the Heart Beat,* 3rd ed., p. 611. Lea and Febiger, Philadelphia.

Bernreiter, M. (1956). Unusual electrocardiographic findings in cardiac amyloidosis. *Journal of the American Medical Association,* **161,** 441.

Chung, K. Y., Walsh, T. J., and Massie, E. (1964). Electrical alternans; a report of 12 cases. *American Journal of the Medical Sciences,* **248,** 212–220.

Colvin, J. (1958). Electrical alternans: case report and comments on the literature. *American Heart Journal,* **55,** 513–517.

Gavrilescu, S., Cotoi, S., and Pop, T. (1973). Monophasic action potential of the right atrium in paroxysmal atrial flutter and fibrillation. *British Heart Journal,* **35,** 585–589.

Hamburger, W. W., Katz, L. N., and Saphir, O. (1935). Electrical alternans—a clinical study with a report of two necropsied cases. *Transactions of the Association of American Physicians,* **50,** 310–334.

Hoffman, B. F., and Cranefield, P. F. (1960). *Electrophysiology of the Heart,* p. 42. McGraw-Hill, New York.

Hoffman, B. F., Cranefield, P. F., Lepeschkin, E., Surawicz, B., and Herrlich, H. C. (1959). Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. *American Journal of Physiology,* **196,** 1297–1301.

Hoffman, B. F., and Singer, D. H. (1964). Effects of digitalis on electrical activity of cardiac fibers. *Progress in Cardiovascular Diseases,* **7,** 226–260.

Hoffman, B. F., and Suckling, E. E. (1954). Effect of heart rate on cardiac membrane potentials and the unipolar electrogram. *American Journal of Physiology,* **179,** 123–130.

Hogan, P. M., and Davis, L. D. (1968). Evidence for specialized fibers in the canine right atrium. *Circulation Research,* **23,** 387–396.

Kisch, B. (1949). Auricular alternation after propyl-thiouracil. *Experimental Medicine and Surgery,* **7,** 173–176.

Kleinfeld, M., Stein, E., and Magin, J. (1956). Electrical alternans in single ventricular fibers of the frog heart. *American Journal of Physiology,* **187,** 139–142.

Kohlhardt, M. (1975). Transmembranäre Einwärtsströme bei der Erregung des Herzens. *Klinische Wochenschrift,* **53,** 1089–1099.

Levine, H. D. (1966). The clinical diagnosis of PAT with block. In *Mechanisms and Therapy of Cardiac Arrhythmias,* p. 117. Ed. by L. S. Dreifus, W. Likoff, and J. H. Moyer. Grune and Stratton, New York and London.

Lewis, T. (1910). Notes upon alternation of the heart. *Quarterly Journal of Medicine,* **4,** 141–144.

Ling, G., and Gerard, R. W. (1949). The normal membrane potential of frog sartorius fibers. *Journal of Cellular and Comparative Physiology,* **34,** 383–396.

Olsson, S. B. (1971). Monophasic action potentials from right atrial muscle recorded during heart catheterization. *Acta medica Scandinavica,* **190,** 369–379.

Olsson, S. B., Varnauskas, E., and Korsgren, M. (1971). Further improved method for measuring monophasic action potentials of the intact human heart. *Journal of Electrocardiology,* **4,** 19–23.

Piso, H. J. (1956). Elektrische alternans bij aandoeningen van het pericardium. *Nederlandsch Tijdschrift voor Geneeskunde,* **100,** 3874–3880.

Pop, T., Fleischmann, D., and Effert, S. (1976). The recording of the human right atrial monophasic action potential. In *Cardiac Pacing,* p. 80. Ed. by B. Lüderitz. Springer Verlag, Heidelberg.

Reuter, H. (1975). Inward calcium current and activation of contraction in mammalian myocardial fibers. In *Basic Functions of Cations in Myocardial Activity,* p. 13. Ed. by A. Fleckenstein and N. S. Dhalla. University Park Press, Baltimore.

Schamroth, L., Segal, F., and Rabinowitz, D. (1959). Electrical alternans with unusual features. *American Heart Journals,* **58,** 900–904.

Schütz, E. (1936). Elektrophysiologie des Herzens bei einphasischer Ableitung. *Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie,* **38,** 493–620.

Spang, K. (1957). *Rhythmusstörungen des Herzens. Systematik, Ursache und klinische Bedeutung, Therapie,* p. 160. G. Thieme Verlag, Stuttgart.

Zipes, D. P. (1976). Recent observations supporting the role of slow current in cardiac electrophysiology. In *The Conduction System of the Heart. Structure, Function and Clinical Implications,* p. 85. Ed. by H. J. J. Wellens, K. Lie, and M. J. Janse. H. E. Stenfert Kroese B.V., Leiden.

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Two-stage replacement of tricuspid valve in active endocarditis

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One month after a 21-year-old female drug addict with tricuspid staphylococcal endocarditis seemed to have been cured by antibiotic therapy she relapsed. Further antibiotic treatment for one month failed to control the infection. Tricuspidectomy was then performed and the infection was eliminated. A valve prosthesis was inserted 3 months later. She recovered and is now fully restored to health. We recommend this two-stage surgical technique in similar cases.

Right-sided endocarditis, mainly involving the tricuspid valve, is no longer a rare disease, its frequency increasing from less than 5 per cent (Thayer, 1931; Bain *et al.*, 1958) to 10 to 20 per cent in the past decade (Roberts and Buchbinder, 1972; Arbulu *et al.*, 1973); this can be ascribed largely to the increased incidence of narcotic addiction (Conway, 1969; Banks *et al.*, 1973; Graham *et al.*, 1973; Svanbom *et al.*, 1973).

Valve replacement during the active stage of endocarditis is now an accepted form of treatment in many places (Strandell *et al.*, 1969; Manhas *et al.*, 1972; Graham *et al.*, 1973; Black *et al.*, 1974), but not in all. Good results have been obtained in many cases of tricuspid valve endocarditis by means of valve resection alone (Arbulu *et al.*, 1973; Graham *et al.*, 1973, Michl *et al.*, 1973) or with the insertion of an artificial valve at a second operation (Arbulu *et al.*, 1973; Simberkoff *et al.*, 1974).

Case report

The patient was a 21-year-old woman without known heart disease, who had taken narcotics intravenously for about 4 years. Some weeks before the onset of the present illness, she had an infection in one foot after treading on a piece of glass.

On 14 June 1974 during a holiday abroad, she fell ill with malaise and fever above 40°C and was treated with antibiotics. On returning to Sweden on 24 June, she was admitted to Roslagstull Hospital for persisting high fever.

On admission she was febrile, but had no signs of cardiac failure or peripheral emboli. A systolic murmur grade 2/6 was heard over the apex. The liver and spleen were enlarged. *X*-ray film showed infiltrations in the right middle and left lower lung lobes. Electrocardiogram was normal apart from sinus tachycardia. Phonocardiogram showed a faint systolic murmur of medium frequency, thought, however, to be consistent with a normal flow in the pulmonary artery.

On the third day in hospital a growth of penicillinase-producing *Staphylococcus aureus* from blood was reported and cloxacillin plus benzyl penicillin were administered. On the next day, she became dyspnoeic and *x*–ray examination showed a pleural effusion. Despite changes in antibiotic therapy, the lung shadows increased with cavity formation in the right lower lobe.

On 15 July, transient murmurs and electrocardiographic abnormalities suggestive of pericarditis were noted and pulmonary scintigraphy indicated changes consistent with multiple small emboli. Right-sided cardiac catheterisation showed normal pressures. Angiocardiography defined a walnut-sized mass on the tricuspid valve, with extreme regurgitation.

After further antibiotic treatment, the patient was discharged on 1 October, afebrile and asymtomatic, but was readmitted on 28 October with fever and cough. A chest *x*-ray film showed further infiltration and scintigraphy revealed fresh infarction of the left lower lobe. The heart size had increased from 300 to 400 ml per m^2 body surface area. The electrocardiogram was initially normal but signs of right ventricular strain appeared later. Though repeated blood cultures were negative, carbenicillin and gentamicin were given and the temperature subsided.

On 25 November, the tricuspid valve was resected under total cardiopulmonary bypass at the Thoracic Surgical Clinic, Karolinska sjukhuset, Stockholm. Large vegetations were seen on the posterior leaflet with acute inflammatory reaction. Bacteria were not seen on microscopy or cultured. Increased pulsation of the jugular veins and the liver was noted after operation. Right heart catheterisation showed a low stroke volume, normal pressures in the pulmonary capillary venous and pulmonary arterial positions, and a high right ventricular end-diastolic pressure. Heart size was now 510 ml per m^2 body surface area. She was dyspnoeic on walking but otherwise felt well.

On account of the persistent right-sided failure, a 31 mm Björk-Shiley mitral valve prosthesis was inserted on 12 February 1975, and 15 days later she was discharged. One year after operation, she was in good health, working full-time, and had resumed water-skiing.

Discussion

The combination of narcotic addiction, staphylococcal septicaemia with right-sided endocarditis, and pulmonary embolism was first described by Hussey *et al.* (1944), and has often been reported since then (Hussey and Katz, 1950; Olsson and Romansky, 1962; Conway, 1969; Roberts and Buchbinder, 1972; Menda and Gorbach, 1973; Svanbom *et al.*, 1973). These authors drew attention to the possibility of tricuspid valve involvement. In this form of endocarditis cardiac symptoms are initially often obscure (Bain *et al.*, 1958; Conway, 1969; Arbulu *et al.*, 1973; Graham *et al.*, 1973), and the diagnosis and treatment may be delayed. Later in the course of the disease, typical signs of tricuspid regurgitation (Banks *et al.*, 1973) and increasing heart size are frequent. These symptoms were observed in our patient and the diagnosis was also verified by right-sided ventriculography.

Staphylococci are still the most common agents in this connection (Roberts and Buchbinder, 1972; Banks *et al.*, 1973; Graham *et al.*, 1973; Menda and Gorbach, 1973), but in recent years other organisms, particularly Gram-negative bacilli, have also been implicated (Carruthers and Kanokvechayant, 1973; Graham *et al.*, 1973; Rosenblatt *et al.*, 1973). Mixed infections have also been reported (Menda and Gorbach, 1973; Simberkoff *et al.*, 1974).

Staphylococcal tricuspid endocarditis may respond to antibiotic therapy alone (Arbulu *et al.*, 1973; Menda and Gorbach, 1973), and initially this seemed to apply in our case as the patient was discharged apparently without active infection, after 10 weeks of antibiotic treatment. Her second illness with fever and pulmonary emboli suggested reactivation of her endocarditis. The signs of acute inflammatory reaction in the excised valve supported this suggestion but the aetiology of the relapse remained obscure since repeated blood cultures were negative and examination of the excised valve gave no indication of the causative agent.

Infectious foci in heart valves are difficult to treat. The bacteria may acquire resistance to the antibiotics, or L–forms of the bateria may develop. In our case, a superinfection may have occurred when the patient may have been giving herself injections. A 'mixed' infection with Gram-negative bacteria in addition to staphylococci (Simberkoff *et al.*, 1974) may have developed. The favourable effect of gentamicin and carbenicillin supports this.

The primary treatment of bacterial endocarditis is conservative. Surgical intervention was used only for patients with haemodynamic failure after healed endocarditis (Yeh *et al.*, 1964), until Wallace *et al.* (1965) for the first time operated during the active stage of endocarditis when conservative treatment had failed. Since then several similar reports have been published (Strandell *et al.*, 1969; Manhas *et al.*, 1972; Graham *et al.*, 1973; Black *et al.*, 1974). The favourable results tally with the well-known fact that the elimination of infected foci is important for the successful treatment of septicaemia.

Valve replacement during active endocarditis is not always successful, and there are reports of paraprosthetic endocarditis and failure of sutures (Manhas *et al.*, 1972). Consequently, a decision on surgical intervention must not be premature, and should only be undertaken when antibiotic treatment has been shown to be ineffective. On the other hand, the probabilities of left heart involvement and toxic myocarditis increase with time. Arbulu *et al.* (1973) recommend surgical intervention when antibiotic treatment has not healed the infection within 6 weeks.

The small pressure differences within the right heart make damage to its valvular system less detrimental than such damage to the left heart. Traumatic tricuspid damage, which persisted for several decades without any symptoms, has been described previously (Croxson *et al.*, 1971; Morgan and Forker, 1971; Marvin *et al.*, 1973). In the series of Arbulu (Arbulu *et al.*, 1973) during a follow-up time of 3 to 27 months, only 1 of 10 survivors required insertion of a prosthetic valve. However, experience from animal experiments (Spellman and Balkissoon, 1956; Michl *et al.*, 1973), from traumatic tricuspid regurgitation, and from patients with valve resections (Michl *et al.*, 1973; Robin *et* *al.*, 1974), indicates that right heart failure may develop sooner or later.

Adaptation to tricuspid regurgitation in young and otherwise healthy persons with normal pulmonary resistance may be considerable, but the insertion of a prosthesis could result in completely normal haemodynamic function. Our patient is now working full time and water skis, which is indicative of good haemodynamic function.

We consider that tricuspid valve replacement is safe when a low profile prosthesis with optimal haemodynamic properties, such as the Björk-Shiley valve, is used.

References

Arbulu, A., Kafi, A., Thoms, N. W., and Wilson, R. F. (1973). Right-sided bacterial endocarditis. *Annals of Thoracic Surgery*, **16**, 136–140.

Bain, R. C., Edwards, J. E., Scheifley, C. H., and Geraci, J. E. (1958). Right-sided bacterial endocarditis and endarteritis. A clinical and pathologic study. *American Journal of Medicine*, **24**, 98–110.

Banks, T., Fletcher, R., and Ali, N. (1973). Infective endocarditis in heroin addicts. *American Journal of Medicine*, **55**, 444–451.

Black, S., O'Rourke, R. A., and Karliner, J. S. (1974). Role of surgery in the treatment of primary infective endocarditis. *American Journal of Medicine*, **56**, 357–369.

Carruthers, M. M., and Kanokvechayant, R. (1973). *Pseudomonas aeruginosa* endocarditis. Report of a case, with review of the literature. *American Journal of Medicine*, **55**, 811–818.

Conway, N. (1969). Endocarditis in heroin addicts. *British Heart Journal*, **31**, 543–545.

Croxson, M. S., O'Brien, K. P., and Lowe, J. B. (1971). Traumatic tricuspid regurgitation. Long-term survival. *British Heart Journal*, **33**, 750–755.

Graham, D. Y., Reul, G. J., Martin, R., Morton, J., and Kennedy, J. H. (1973). Infective endocarditis in drug addicts. Experiences with medical and surgical treatment. *Circulation*, **47** and **48**, Suppl. III, 37–41.

Hussey, H. H., and Katz, S. (1950). Infections resulting from narcotic addiction. *American Journal of Medicine*, **9**, 186–193.

Hussey, H., Keliher, T. F., Schaefer, B. F., and Walsh, B. J. (1944). Septicemia and bacterial endocarditis resulting from heroin addiction. *Journal of the American Medical Association*, **126**, 535–538.

Manhas, D. R., Mohri, H., Hessel, E. A., and Merendino, K. A. (1972). Experience with surgical management of primary infective endocarditis. A collected review of 139 patients. *American Heart Journal*, **84**, 738–747.

Marvin, R. F., Schrank, J. P., and Nolan, S. P. (1973). Traumatic tricuspid insufficiency. *American Journal of Cardiology*, **32**, 723–726.

Menda, K. B., and Gorbach, S. L. (1973). Favourable experience with bacterial endocarditis in heroin addicts. *Annals of Internal Medicine*, **78**, 25–32.

Michl, L., Shumacker, H. B., and Hobbs, D. (1973). Tricuspid valvulectomy. *Surgery, Gynecology and Obstetrics*, **137**, 590–592.

Morgan, J. R., and Forker, A. D. (1971). Isolated tricuspid insufficiency. *Circulation*, **43**, 559–564.

Olsson, R. A., and Romansky, M. J. (1962). Staphylococcal tricuspid endocarditis in heroin addicts. *Annals of Internal Medicine*, **57**, 755–762.

Roberts, W. C., and Buchbinder, N. A. (1972). Right-sided valvular infective endocarditis. A clinicopathologic study of twelve necropsy patients. *American Journal of Medicine*, **53**, 7–19.

Robin, E., Belamaric, J., Thoms, N. W., Arbulu, A., and Ganguly, S. N. (1974). Consequences of total tricuspid valvulectomy without prosthetic replacement in treatment of Pseudomonas endocarditis. *Journal of Thoracic and Cardiovascular Surgery*, **68**, 461–465.

Rosenblatt, J. E., Dahlgren, J. G., Fishbach, R. S., and Tally, F. P. (1973). Gram-negative bacterial endocarditis in narcotic addicts. *California Medicine*, **118** (2), 1–4.

Simberkoff, M. S., Isom, W., Smithivas, T., Noriega, E. R., and Rahal, J. J. (1974). Two-stage tricuspid valve replacement for mixed bacterial endocarditis. *Archives of Internal Medicine*, **133**, 212–216.

Spellman, M. W., and Balkissoon, B. (1956). The production and evaluation of ascites secondary to isolated tricuspid insufficiency in dogs. *Surgery*, **39**, 37–48.

Strandell, T., Bengtsson, E., Björk, V. O., Michaeli, E., Svanbom, M., and Tunevall, G. (1969). Fulminant bakteriell endokardit med ruptur av aortaklaffarna, behandlad med aortaprotes under akut stadium. *Nordisk Medicin*, **82**, 1083–1084.

Svanbom, M., Bengtsson, E., Strandell, T., and Tunevall, G. (1973). Septicemia in narcotic addicts. *Scandinavian Journal of Infectious Diseases*, **5**, 97–110.

Thayer, W. S. (1931). Bacterial or infective endocarditis. *Edinburgh Medical Journal*, **38**, 237–265; 307–334.

Wallace, A. C., Young, W. G., and Osterhout, S. (1965). Treatment of acute bacterial endocarditis by valve excision and replacement. *Circulation*, **31**, 450–453.

Yeh, T. J., Hall, D. P., and Ellison, R. G. (1964). Surgical treatment of aortic valve perforation due to bacterial endocarditis. *American Surgeon*, **30**, 766–769.

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British Heart Journal, 1977, **39**, 1279-1281

Myopotential inhibition of a bipolar pacemaker caused by electrode insulation defect

S. AMIKAM, H. PELEG, J. LEMER, AND E. RISS

From the Departments of Cardiology and Cardiac Surgery, Rambam Medical Center, Aba Khoushy School of Medicine, Haifa, Israel

A patient is described in whom myopotentials originating from the anterior abdominal wall muscles suppressed the implanted demand pacemaker despite its bipolar mode of action. This phenomenon was shown by simultaneous recording of the electrocardiogram and the electromyogram. At operation, a defect in the insulation of a previously repaired epicardial electrode was found lying in close proximity to these muscles. After repair of the insulation defect, normal pacemaker function was restored. It is suggested that the myopotentials leaked into the pacing system through the insulation defect, thereby suppressing the demand unit, which maintained its bipolar mode of pacing throughout.

It is now well established that potentials from skeletal muscles are capable of inhibiting demand unipolar pacemaker function (Wirtzfeld *et al.*, 1972; Mymin *et al.*, 1973; Ohm *et al.*, 1974). The long single electrode configuration presents a large dipole to which myopotentials (Piller and Kennelly, 1974), as well as electromagnetic fields from the surrounding environment (Sowton *et al.*, 1970), may be induced causing pacemaker inhibition. Bipolar demand systems are not prone to myopotential inhibition because the relative proximity of the electrodes gives a lower potential difference between the poles.

The purpose of this case report is to describe a patient in whom an insulation defect of one epicardial electrode allowed abdominal wall muscle potentials to suppress pacemaker function, despite the bipolar nature of the pacing system.

Case report

A 58-year-old woman had a permanent bipolar epicardial pacemaker implantation in 1965 for complete heart block and Adams-Stokes attacks. Since then the pacemaker generator has been electively replaced four times. The units had always been placed in the subcutaneous tissue of the anterior abdominal wall. During replacement of the fourth unit in 1973, one of the epicardial leads was erroneously transected and was immediately repaired. The repair was carried out by removing the insulation adjacent to the transected ends, intertwining the bared ends of the electrode coil, and reconstituting the insulation with a silicone adhesive-filled Silastic sleeve. The patient's subsequent course was uneventful and the pacemaker functioned well for a further 3 years, when a Medtronic demand bipolar model 5950 was electively implanted in June 1976. Four months later, the patient presented with signs of early erosion of the skin overlying the pacemaker unit. She underwent reimplanation of the same unit to a more medial position and in addition deep to the sheath of the rectus abdominis muscle.

On the day of operation, electrocardiographic monitoring showed periods of irregular pacing with lack of pacemaker spikes. Further analysis revealed that the pacemaker was intermittently inhibited, with the appearance of junctional escape beats (Fig. 1). This disturbance did not appear while the patient lay completely at rest and could be evoked again whenever the patient was asked to cough, to do a Valsalva manoeuvre, or to rise from a supine to a sitting position, i.e. while activating the abdominal wall muscles. However, the patient remained symptomless as she was resting in bed and because of the presence of escape beats which prevented long asystolic periods. Converting the pulse generator to the fixed-rate mode by external application of a magnet prevented this phenomenon during these exercises.

In order to demonstrate the mechanism of this interference, in addition to the electrocardiogram, an electromyogram from the left rectus abdominis muscle was simultaneously recorded during rest and during the above-mentioned manoeuvres (Fig. 2). It became evident that the pacemaker inhibition occurred only during rectus abdominis activation and was effectively corrected by the application of a magnet, changing the demand mode to a fixed-rate pacing.

On exposure at operation of the previously repaired epicardial electrode in the anterior abdominal wall, a defect was found in its insulation at the site of the repair. The proximal end of the Silastic sleeve surrounding the repair was not adherent and there was a small hole in the hardened silicone adhesive in which the repaired electrode wire was embedded. On squeezing the electrode, a small quantity of fluid escaped through this defect in the insulation. The hole was sealed with additional silicone adhesive, the original defective Silastic sleeve was repaired with adhesive and silk ligatures and finally a second Silastic sleeve was applied to surround the entire repair.

As a result of this procedure normal pacing was achieved, and since then suppression of pacing has not occurred either spontaneously or during abdominal wall muscle activation.

Discussion

Suppression of pacing in this patient occurred during abdominal wall muscle activation as shown by the simultaneous recording of the electrocardiogram and the electromyogram. Presumably the myopotentials were transmitted via the defect in the insulation of the electrode, which was in close proximity to the muscles of the anterior abdominal wall. This electrical activity was sensed by the demand unit and inhibited normal pacing. However, there appeared to be no outward escape of the pacing current through the defect in insulation, as had this occurred, twitching of the abdominal wall muscles would have been noted concomitant with pacemaker stimuli.

As mentioned previously, demand pacemaker units of the bipolar type are not subject to inhibition by myopotentials, this disturbance being strictly confined to the unipolar type. The occurrence of this type of malfunction in a bipolar demand pacemaker is most unusual. We were only able to find one published case report of an implanted bipolar demand pacemaker, in which pacing was suppressed during skeletal muscle activation. Widlansky and Zipes (1974) described a patient in whom isometric

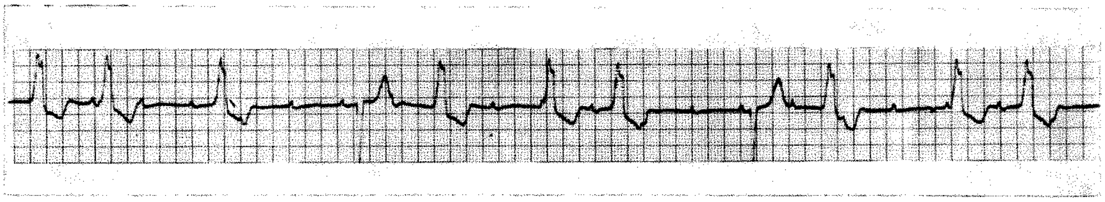

Fig. 1 *Electrocardiographic monitor recording shows irregular pacing with short periods of ventricular asystole and junctional escape beats. Pacemaker spikes are not visible in this tracing.*

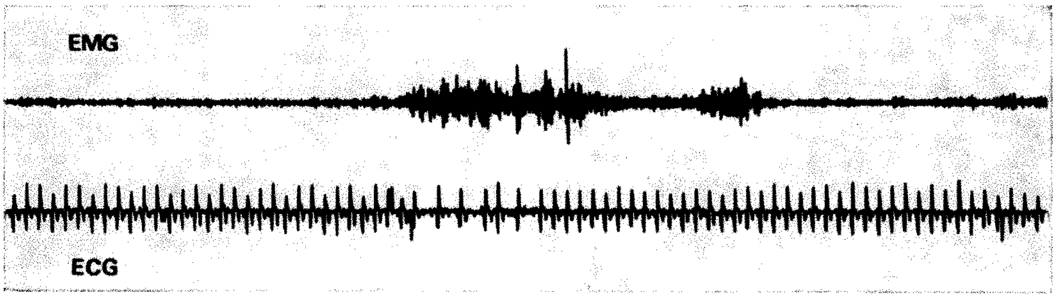

Fig. 2 *Simultaneous recording of the electrocardiogram (lower tracing) and the electromyogram from the rectus abdominis muscle (upper tracing). Paper speed 5 mm per second. It is evident that the period of irregular pacing is concomitant with abdominal muscle activation.*

movements of the right pectoral muscle group totally suppressed bipolar demand pacemaker discharge. In their case, which had been paced by an endocardial electrode, it was discovered at operation that a proximal end of one of the electrodes was not correctly seated in the pulse-generator, and fluid had leaked into the connector boot. The authors suggested two possible explanations for the muscle-induced pulse-generator inhibition: (1) conversion of the bipolar demand system to a unipolar demand system by the fluid leak with subsequent sensing of myopotentials; and (2) generation of false (make-break) electrical signals from repetitive interruption of the electrical circuit, caused by pectoral muscle activity, which were sensed by the demand unit, thereby suppressing its function. The authors tended to favour the second explanation as the pacemaker spikes remained unchanged before and after correction of the fault, indicating that unipolar pacing had not occurred during the period of malfunction.

The two possibilities cited cannot adequately explain the inhibition of pacing in our patient. We did not record on the electrocardiogram any change in the axis or amplitude of the pacemaker spike or in the paced QRS complexes during all stages of our patient's management. Therefore, conversion to a unipolar system did not occur. False (make-break) potentials could not have occurred in our patient, as electrode wire continuity was clearly shown along its entire length, both on *x*-ray film and at operation. We propose that the pacemaker inhibition in our patient was the result of a leakage of abdominal muscle myopotentials into the pacing system through the defect in the electrode insulation which was in close proximity to the muscles. This malfunction occurred without the conversion of the pacemaker system to a unipolar mode.

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References

Mymin, D., Cuddy, T. E., Sinha, S. N., and Winter, D. A. (1973). Inhibition of demand pacemakers by skeletal muscle potentials. *Journal of the American Medical Association*, **223**, 527–529.

Ohm, O. J., Bruland, H., Pedersen, O. M., and Waerness, E. (1974). Interference effect of myopotentials on function of unipolar demand pacemakers. *British Heart Journal*, **36**, 77–84.

Piller, L. W., and Kennelly, B. M. (1974). Myopotential inhibition of demand pacemakers. *Chest*, **66**, 418–420.

Sowton, E., Gray, K., and Preston, T. (1970). Electrical interference in non-competitive pacemakers. *British Heart Journal*, **32**, 626–632.

Widlansky, S., and Zipes, D. P. (1974). Suppression of a ventricular-inhibited bipolar pacemaker by skeletal muscle activity. *Journal of Electrocardiology*, **7**, 371–374.

Wirtzfeld, A., Lampadius, M., and Ruprecht, E. O. (1972). Unterdrückung von Demand-Schrittmachern durch Muskelpotentiale. *Deutsche medizinische Wochenschrift*, **97**, 61–66.

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Notices

British Heart Journal, 1977, **39,** 1282

National Conference on High Blood Pressure Control

This conference will be held at Los Angeles Hilton, Los Angeles, California, 2-4 April 1978. For further information write to:

Ms. Julie Knowles, Abstract Coordinator,
Conference Headquarters,
National Conference on High Blood Pressure Control,
1501 Wilson Boulevard, Suite 600,
Arlington,
Virginia 22209,
U.S.A.

International Symposium on Primary Prevention in Childhood of Atherosclerotic and Hypertensive Diseases

The symposium will be held at Ambassador West Hotel, Chicago, Illinois, on 18, 19, and 20 October 1978. For further information write to:

Susan Shekelle,
Chicago Heart Association,
20 North Wacker Drive,
Room 1240,
Chicago,
Illinois 60606,
U.S.A.

European Society of Cardiology First Joint Meeting of the Working Groups, 22-25 June 1978

The object of the meeting at the University of Sussex, Brighton, England, is to bring together active scientific workers in cardiology in Europe. The various Working Groups, announced in this Journal, will organise the programme.

Anybody may participate, whether or not they are formally members of a Working Group. Admission will be free, but attendance will be limited to 1300 and registration is necessary. About 800 single rooms are available on the campus and an indivisible 'package' will be offered for meals and accommodation for four nights at approximately £45. These will be allocated first-paid-first-served until 1 May 1978. There are hotels in Brighton for those preferring individual arrangements.

The official languages are French and English, with no translations. There will be no social programme and no added expenses.

Deadline for submission of abstracts of communications is 1 February 1978.

For further information and abstract forms, write to the Chairmen of the Working Groups or to Professor Paul G. Hugenholtz, Thoraxcenter, University Hospital Rotterdam, P.O. Box 23102, Rotterdam, The Netherlands.

Fifth Scientific Meeting of the International Society of Hypertension

This will be held in Maison de la Chimie (Paris), 12, 13, and 14 June 1978. For further information write to:

Local Organizing Scientific Committee,
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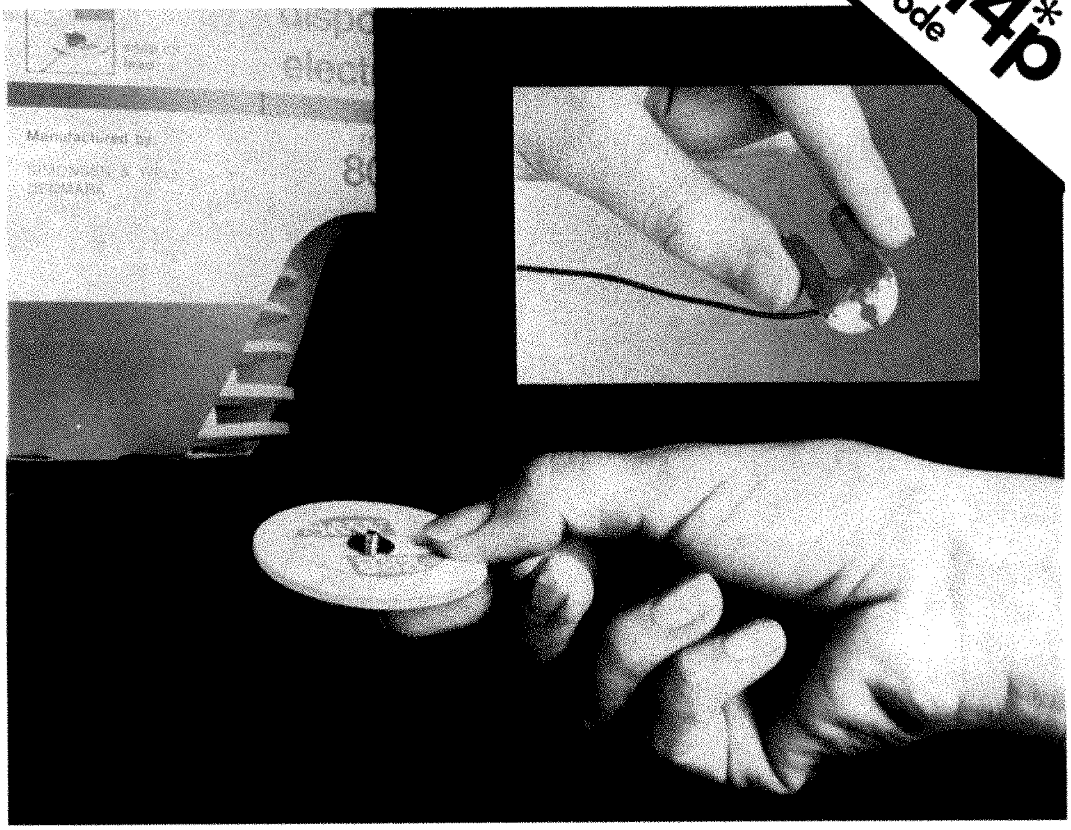

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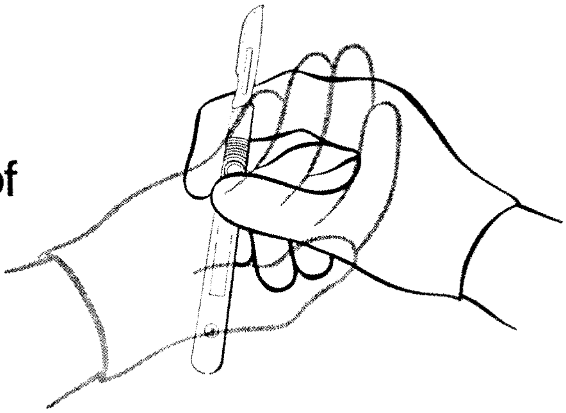

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1. Postgrad. Med. J., 51, 10, (1975)
2. Danish Med. Bull., 21, 63, (1974)
3. Clin. Pharm. Ther., 15, 141, (1974)
4. J. Int. Med. Res., 2, 314, (1974)
5. Brit. J. Clin. Prac., 28, 311, (1974)
6. Brit. J. Clin. Prac., 29, 7, (1975)
7. Postgrad. Med. J., 51, (Suppl. 6), 54, (1975)
8. Brit. J. Clin. Prac. 30, 11-14 (1976)
9. Leading Article, Brit. Med. J., 2, 521, (1975)
10. J. Int. Med. Res., 3, 241, (1975)
11. Postgrad. Med. J., 51, (Suppl. 6), 71, (1975)
12. Acta. Med. Scand., 193, 119, (1973)
13. J. Int. Med. Res., 3, 104, (1975)
14. J. Int. Med. Res., 4, 37-41 (1976)

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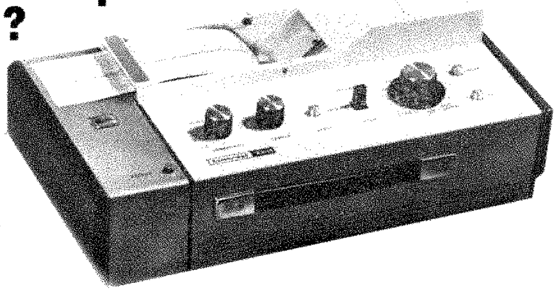

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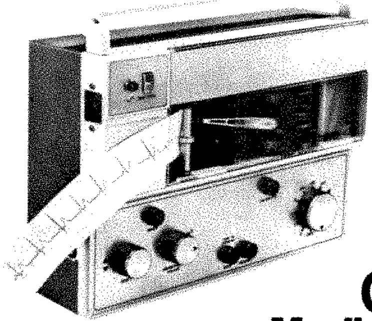

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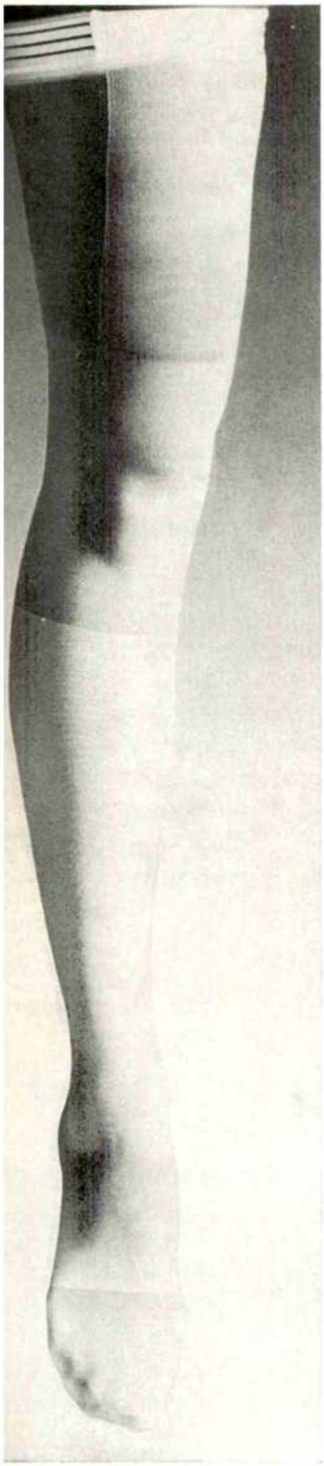

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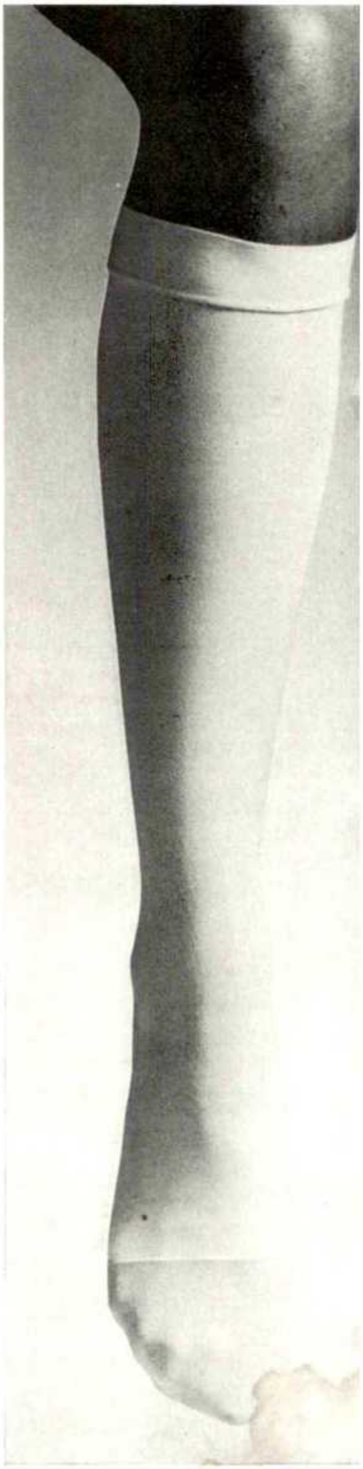

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4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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References 1. *Concepts in the treatment of hypertension, Excerpta Medica*, Amsterdam, 1977, p 66.
2. *Europ. J. Clin. Pharmacol.*, 1976, **10**, 375

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Thromboembolism

A New Approach to Therapy

edited by J. R. A. Mitchell and J. C. Domenet

December 1977, xii + 200pp., £5·60/$11·00

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This book contains the proceedings of a conference held in London in September 1976. Attention was focused on the role of blood platelets in the processes of thrombus formation, thrombosis and thromboembolism—the conditions underlying major cardiovascular disorders including stroke, pulmonary embolism and coronary diseaee. At present, only secondary prevention is practised, but since platelet function can now be modified by drug therapy, there is potential for primary prevention of these serious diseases. Hence the "new approach" of the title. Consideration has also been given to the prevention or treatment of clotting tendencies in certain special situations such as renal dialysis, heart-lung machines, and haemoperfusion for liver conditions. In reviewing progress to date and in presenting and discussing findings of research and clinical studies, the book is designed to present basic information to practising clinicians in all fields of medicine, surgery, and haematology, and to those working in the research field. In finishing with a look at future prospects, this review, in conjunction with the introductory "keynote lecture", puts the whole subject of thromboembolism into long-term perspective.

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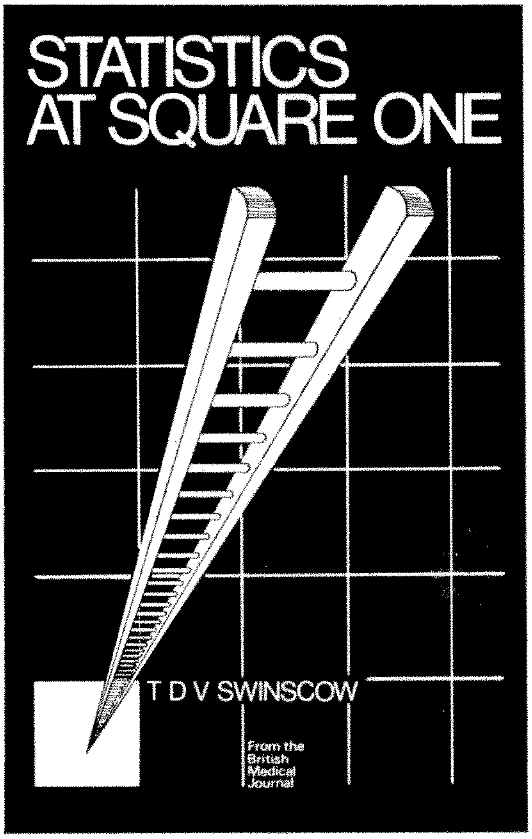

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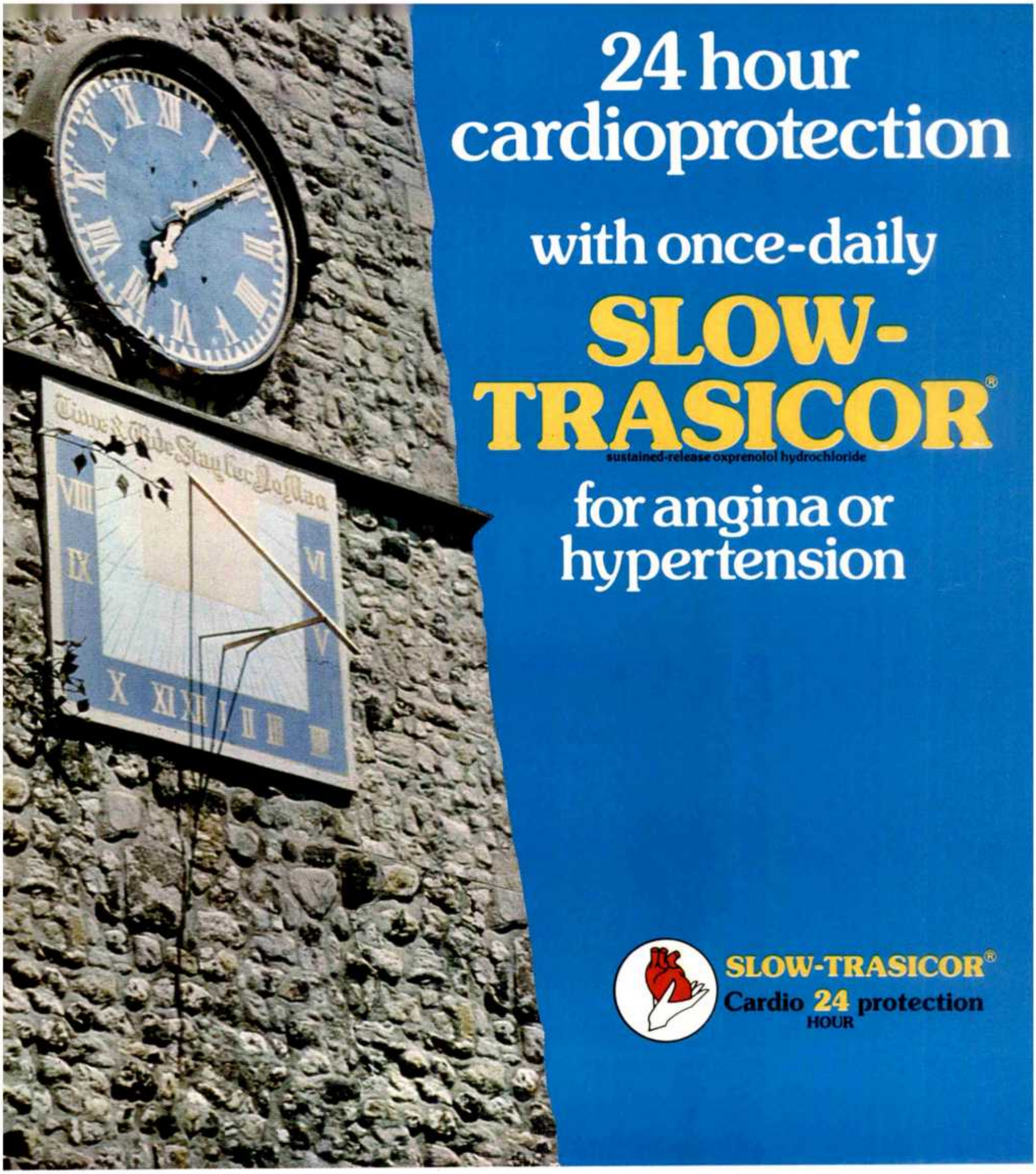
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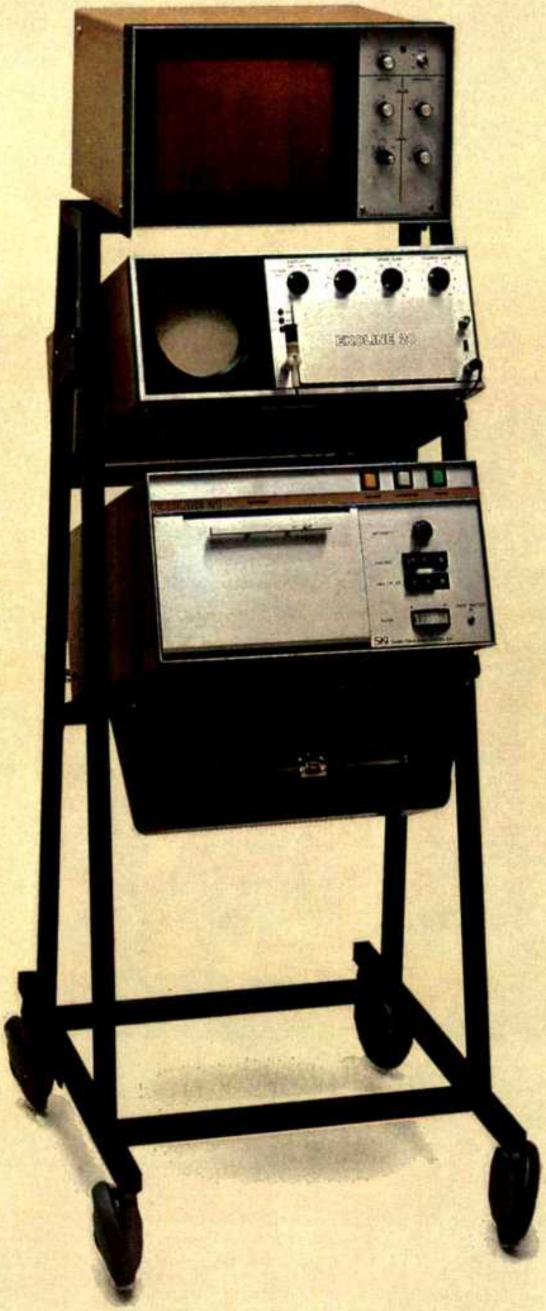

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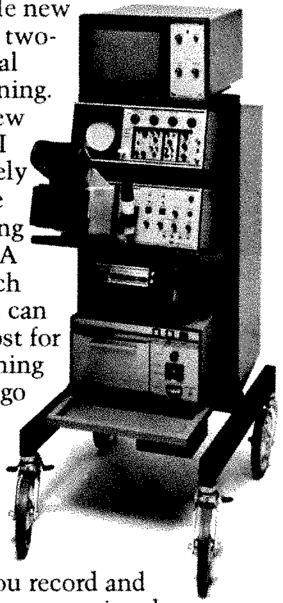

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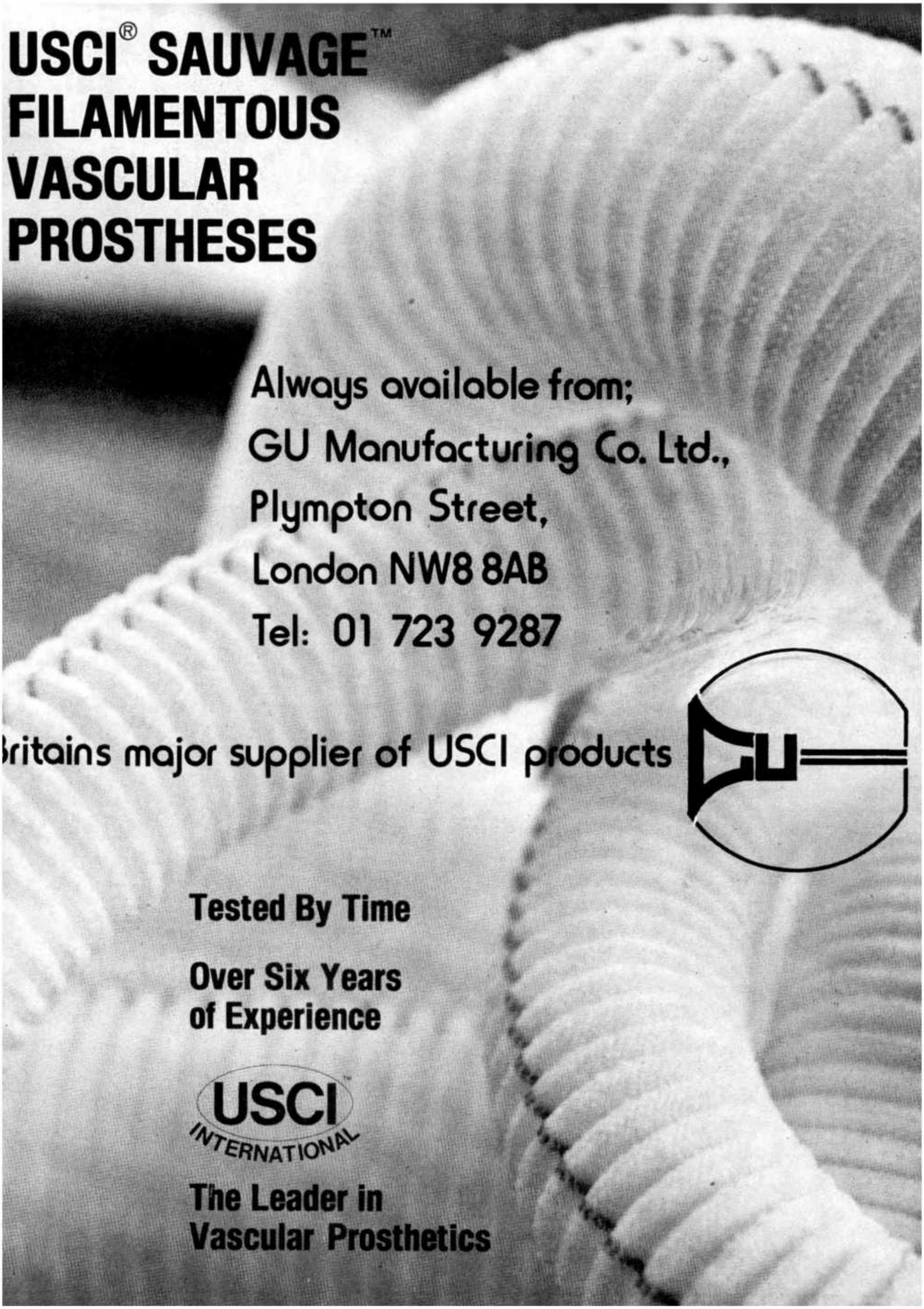**USCI® SAUVAGE™
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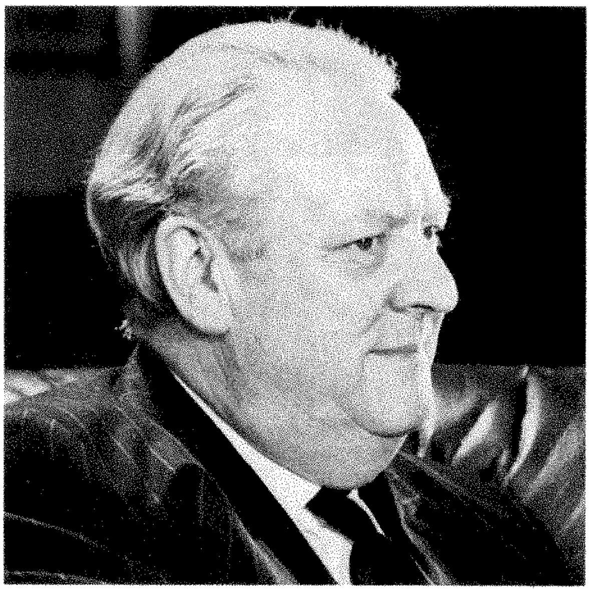

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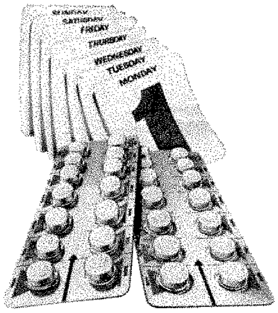

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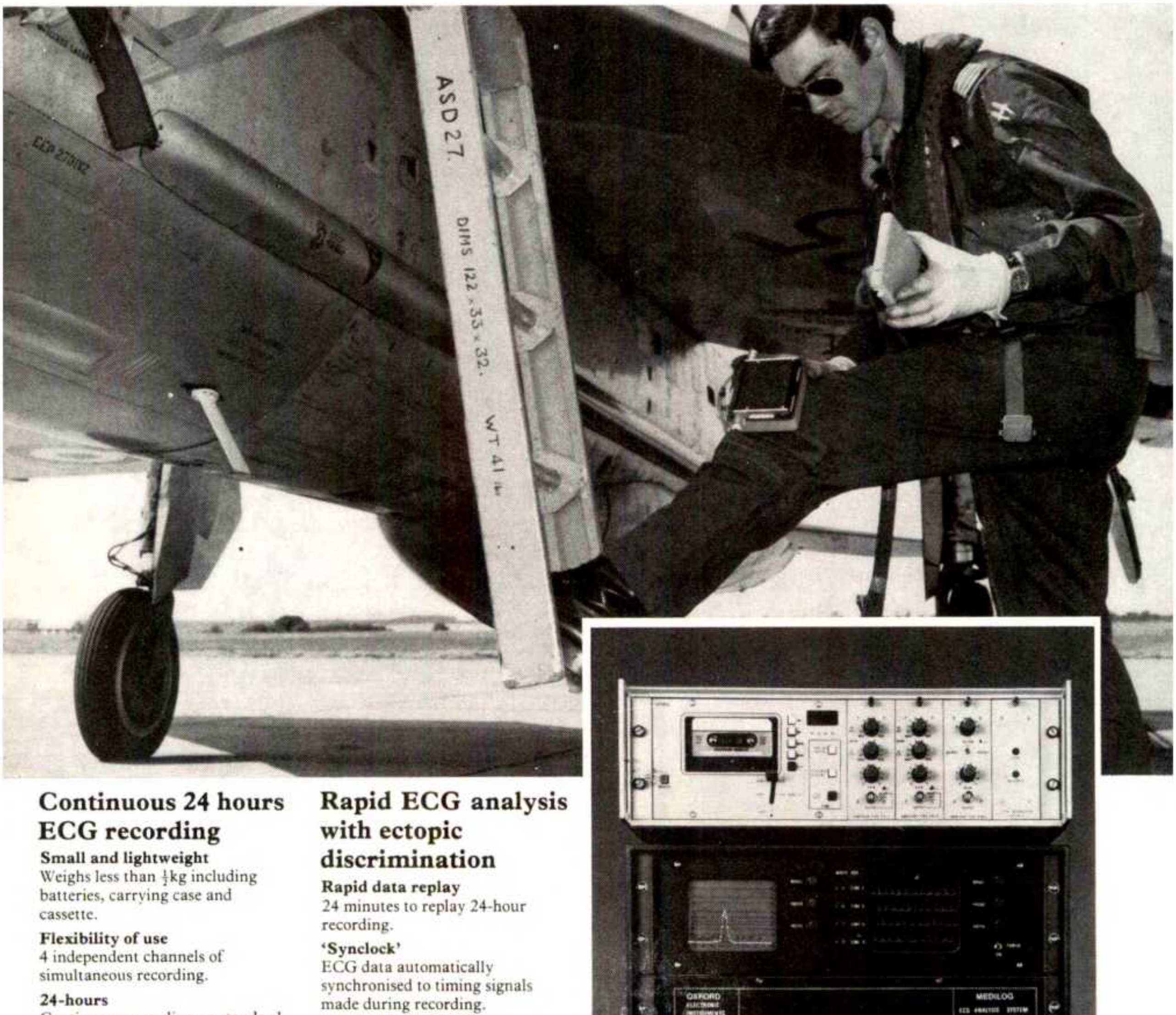
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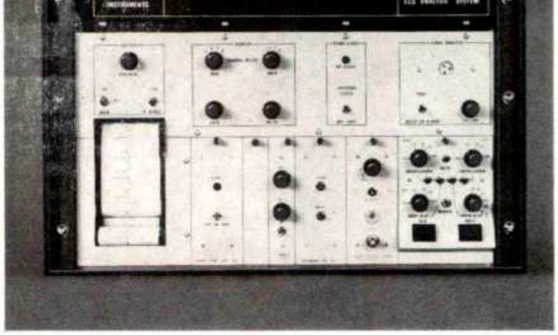

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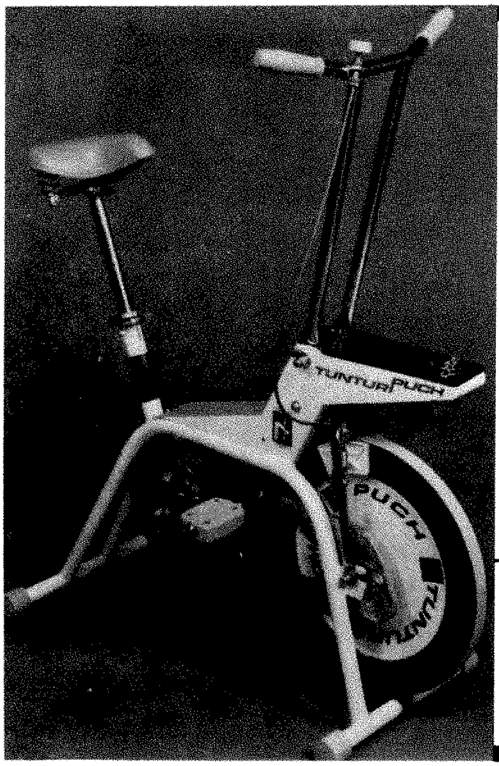

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D. J. BROWN, AND D. G. GIBSON

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In order to investigate the functional effects of mitral valve surgery, echocardiograms showing left ventricular dimension were recorded and digitised in 14 normal subjects and 129 patients after mitral valve surgery. Measurements were made of peak rate of increase of dimension (dD/dt) and duration of rapid filling, studies on left ventriculograms in 36 patients having shown close correlation between these values and changes in cavity volume. In 14 patients with mitral stenosis, peak dD/dt was reduced to 7·2±1·5 cm/s, and filling period prolonged to 330±65 ms, compared with normal (16·0±3·2 cm/s, and 160±50 ms, respectively), and after mitral valvotomy, these values improved significantly (10·4±2·7 cm/s and 245±55 ms). Characteristic abnormalities were found in 67 patients with mitral prostheses. Values for the Björk-Shiley (10·5±4·2 cm/s and 180±80 ms) and Hancock (10·3±3·7 cm/s, 245±80 ms) valves were similar, and both superior to the Starr-Edwards (7·4±3·0 cm/s, 295±105 ms). Results after mitral valve repair in 30 cases were not significantly different from normal (14·4±5·0 cm/s, 170±50 ms). Values outside the 95 per cent confidence limits for the valve in question allowed diagnosis of valve malfunction in 18 cases. The method is of value in comparing different operative procedures and in following up patients after mitral valve surgery.

The success of mitral valve repair and replacement is usually judged on clinical grounds and on the results of cardiac catheterisation performed at variable times after operation (Goodale *et al.*, 1955; Morrow *et al.*, 1967). Relief of symptoms and increased exercise tolerance correlate with reduction in pulmonary arterial and left atrial pressures, and with increased cardiac output (Braunwald *et al.*, 1965; Feigenbaum *et al.*, 1968; Hultgren *et al.*, 1968). More recently, echocardiography has made qualitative assessment of the mitral valve possible in terms of cusp thickness and mobility, and characteristic changes have been recorded after mitral valvotomy (Edler, 1967; Effert, 1967; Gustafson, 1967). Mitral prostheses have also been studied using this technique, and the appearance of abnormal echoes or of reduced disc or poppet mobility has confirmed the diagnosis of malfunction (Johnson *et al.*, 1970; Popp and Carmichael, 1971). In the present study, we have attempted to use echocardiography to assess patients postoperatively, not by direct observation of the mitral valve or prosthesis, but by analysis of left ventricular wall movement during diastole. This has allowed us to define specific patterns of wall movement for each of the procedures to the mitral valve, thus establishing a basis for recognition of valve obstruction or regurgitation. In addition, by concentrating on the physiology of ventricular filling, the results can be expressed in a way which allows functional comparison between these different surgical procedures.

Subjects

ECHOCARDIOGRAPHY

Studies were made on 143 patients who fell into 6 groups.

Group 1

Fourteen patients with mitral stenosis underwent closed mitral valvotomy. Eight were women. Their ages ranged from 17 to 45 years. Eight were in sinus rhythm and 6 in atrial fibrillation. Echocardiograms were recorded preoperatively and 3 to 7 days postoperatively.

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Group 2

Thirty patients underwent mitral valve repair. This operation has been described elsewhere (Burr *et al.*, 1976), and involves placing two double semicircular sutures around the mitral valve ring; at the same time, an open commissurotomy may be performed, ruptured chordae corrected, redundant cusp tissue excised, or adherent chordae and papillary muscles separated down the ventricular wall. It was applied, where practicable, to patients with degenerative or rheumatic mitral valve disease, the latter stenotic or regurgitant. Of the 30 patients, 20 were female, their ages ranged from 12 to 73 years. Of the 30 patients 17 had rheumatic mitral valve disease, and 13 had ruptured chordae tendineae or systolic prolapse causing severe mitral regurgitation. Observations were made within 2 years of operation.

Group 3

Thirty patients had normally functioning mitral Starr-Edwards prostheses, and of these 20 were women. Their ages ranged from 18 to 71 years. In 26 patients, mitral valve replacement had been performed for rheumatic mitral valve disease and in 4 for ruptured chordae. Valves of size 3 or 4 composite seat (series 6310 or 6320) or old type (series 6120) were used, and patients were studied between 3 months and 10 years of operation.

Group 4

Thirty patients had normally functioning Björk-Shiley prostheses and of these 16 were female. Their ages ranged from 10 to 68 years. Of the 30 patients, 17 had rheumatic heart disease, 10 had ruptured chordae, and 3 had previous Starr-Edwards prosthetic mitral valve replacement. A size 29 or 31 mm prosthesis was used and patients were studied 3 months to 3½ years after operation.

Group 5

Seven patients had normally functioning Hancock prostheses, and of these 5 were female. Their ages ranged from 15 to 52 years. Four had had rheumatic mitral valve disease, and 3 ruptured chordae tendineae. Patients were studied between 3 months and 2 years of operation.

Group 6

Eighteen patients had evidence of abnormal postoperative valve function. Of these, 14 had a severe paraprosthetic leak associated with a Starr-Edwards prosthesis, 2 had a clotted Björk-Shiley prosthesis, and 2 had abnormal mitral valve function after repair, caused by stenosis in one and by regurgitation in the other. These findings were all confirmed at a second operation.

Normal subjects

Observations were also made in 14 subjects (10 of whom were male) with ages ranging between 13 and 56 with no clinical evidence of heart disease.

ANGIOGRAPHY

Left ventricular angiograms of 36 patients were studied. These fall into three groups.

Group A

Ten patients who complained of chest pain had normal haemodynamics, normal left ventricular function, and normal coronary angiograms at cardiac catheterisation and were referred to as a 'normal' group.

Group B

Ten patients had rheumatic mitral valve disease.

Group C

Sixteen patients had a mitral Starr-Edwards prosthesis, and were reinvestigated because of suspected malfunction. Significant paraprosthetic regurgitation was present in 5 patients.

Methods

ECHOCARDIOGRAPHY

All echocardiograms were made using the Ekoline 20 ultrasonoscope. Recordings were made photographically from a Cambridge multichannel or Honeywell 1856 strip-chart recorder at a paper speed of 100 mm/s, with a simultaneous electrocardiogram. All patients were studied recumbent, and rotated slightly to the left side. Echocardiograms of the left side of the septum and posterior left ventricular wall were obtained at the level of the mitral valve, or just below the level of the prosthesis. Measurements were made only on patients in whom clear continuous echoes were obtained simultaneously from the left side of the septum and posterior wall. Echocardiograms were digitised as described by Gibson and Brown (1973), on a Summagraphics digitising table, and were processed by a Prime 300 computing system. Instantaneous left ventricular dimension (D) and its peak rate of change (dD/dt) (Gibson and Brown, 1973) were derived from the echocardiograms. In the group of patients undergoing mitral valve repair, the echocardiogram of the anterior cusp of the mitral valve during diastole was also recorded and digitised, as previously described by Upton *et al.* (1976). Left ventricular filling pattern was assessed from the value of the peak rate of increase of left ventricular dimension and also from the time interval from minimum dimension until the filling rate had fallen to 20 per cent of its peak value at the end of the rapid filling period.

ANGIOCARDIOGRAPHY

Angiocardiograms were digitised as previously described (Gibson and Brown, 1975). The superimposed outlines of the left ventricular cavity in successive cine frames were displayed on a Tektronix 4010 video display unit, and a cursor was positioned across the cavity, approximately perpendicular to the long axis, at its mid-point, to define a minor dimension. Plots were then made of this minor dimension (D) and its rate of change with time (dD/dt). Cavity volume (V) was derived from projected area by the area length method (Sandler and Dodge, 1968) and its rate of change (dV/dt) also plotted. From these graphs were derived the following: (1) End-diastolic and end-systolic dimensions and volumes; (2) peak diastolic dD/dt and dV/dt; and (3) the time interval between the onset of diastolic increases in dimension and in volume, peak rates of increase, and the time of reduction to 20 per cent peak value (Fig. 1).

The statistical significance of differences between means was assessed by Student's t test.

Results

ANGIOGRAPHY

There was no significant difference between the timing of minimum dimension and of cavity area in any of the patient groups studied. In normal subjects, the peak rate of increase of dimension occurred 170±25 ms after minimum dimension, and the corresponding value for cavity area was 190±15 ms; the difference (20±20 ms) was significant ($P < 0{\cdot}01$). In patients with mitral stenosis, peak rate of increase of dimension occurred at 120±40 ms, and of area 105±40 ms after the respective minimum values, and for patients with mitral prostheses the corresponding figures were 140±40 ms and 120±50 ms; the latter two differences were not statistically significant.

In the group as a whole, there was very close correlation between the time to 20 per cent filling rate as measured from the dimension (TD) and from the area traces (TA) given by the regression equation

$TA = 0{\cdot}99TD + 8$ ms, $r = 0{\cdot}96$, $SEE = 15$ ms (Fig. 2).

Peak filling rate was derived from the area trace as a rate of increase of volume (dV/dt) and was related to peak rate of increase of dimension (dD/dt) in the whole group by the regression equation

Peak $dV/dt = 22$ peak $dD/dt + 340$ ml/s, $r = 0{\cdot}48$, $SEE = 210$ ml/s.

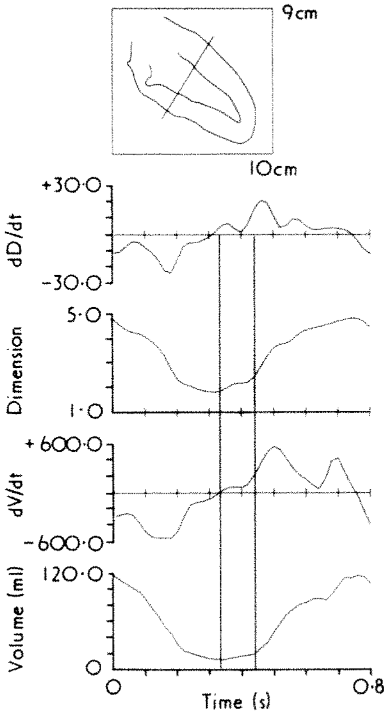

Fig. 1 *Relation between changes in left ventricular volume and transverse dimension in a normal subject, determined from a left ventricular angiogram. From below are shown cavity volume, rate of change of volume, transverse dimension, rate of change of dimension, and (top) end-diastolic and end-systolic cavity outlines, with the position of the dimension indicated. The vertical lines represent minimum cavity area and mitral valve opening.*

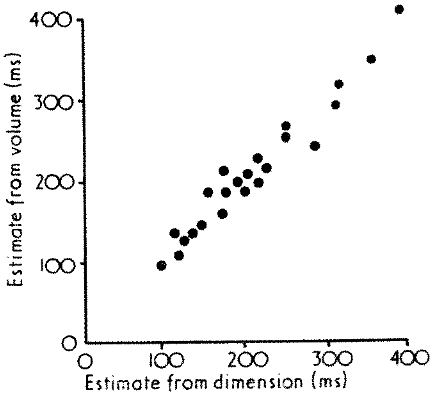

Fig. 2 *Comparison of estimates of time to 20 per cent peak filling rate (left ventricular filling period) from transverse dimension and cavity volume, derived from left ventricular angiograms. There is close correlation between the two.*

When only those patients in whom the left ventricular end-diastolic dimension was less than 6 cm were considered, the equation was

Peak dV/dt = 43 peak dD/dt–50 ml/s, r = 0·81, SEE = 70 ml/s (Fig. 3).

ECHOCARDIOGRAPHY

These results are given in detail in the Table.

Normal subjects

The peak rate of increase of dimension measured from the echocardiogram was 16·0 ± 3·2 cm/s (mean ± 1 standard deviation). This occurred 50 ± 16 ms after the time of minimum dimension, and the rate of increase of dimension had declined to 20 per cent of its peak value by 160 ± 50 ms (Fig. 4). These values, from strip-chart recordings, are similar to but rather higher than those measured from echocardiograms taken on polaroid film at a lower sweep speed (Gibson and Brown, 1973).

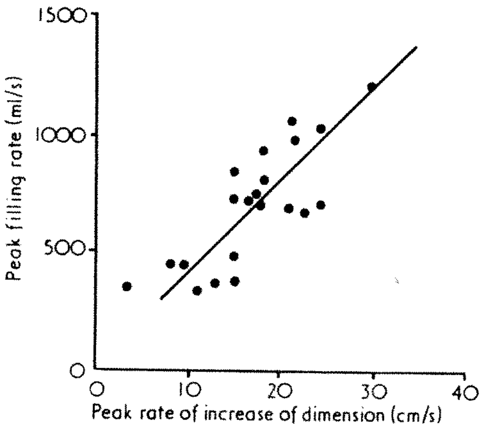

Fig. 3 *Comparison between estimates of peak filling rate and peak rate of increase of transverse dimension in normal patients and those with mitral valve disease or mitral prostheses, in whom end-diastolic transverse dimension was less than 6 cm.*

Table

Valve	*No. of patients*	*Peak dD/dt* (cm/s)*	*Time to 20% peak dD/dt (ms)**
Normal	14	16·0 ±3·2	160 ±50
Mitral stenosis	14	7·2 ±1·5	330 ±65
Mitral valvotomy	14	10·4 ±2·7	245 ±55
Mitral repair	30	14·4 ±5·0	170 ±50
Starr-Edwards	30	7·4 ±3·0	295 ±110
Björk-Shiley	30	10·5 ±4·2	180 ±80
Hancock xenograft	7	10·3 ±3·7	245 ±80
Leaking Starr-Edwards	14	17·0 ±2·0	240 ±60

*Mean values ± standard deviation.

Mitral stenosis

Preoperatively the peak rate of increase of dimension was reduced compared with the normal group to 7·2 ± 1·5 cm/s (P < 0·001), and the filling period significantly prolonged, so that the rate of increase of dimension had not dropped to 20 per cent of its peak value before 330 ± 65 ms (P < 0·001). After operation, the peak rate of increase of dimension had increased to 10·4 ± 2·7 cm/s, which was significantly greater than before operation (P < 0·01), though less than normal (P < 0·01). Similarly, the time to 20 per cent peak filling rate fell to 245 ± 55 ms, significantly less than preoperatively (P < 0·01), though greater than normal (P < 0·01) (Fig. 5). Peak mitral diastolic closing rate was 20 mm/s preoperatively, increasing to 37 mm/s after operation (P < 0·01).

Starr-Edwards prosthesis

The peak rate of increase of dimension was 7·4 ± 3·0 cm/s, significantly less than normal (P < 0·001),

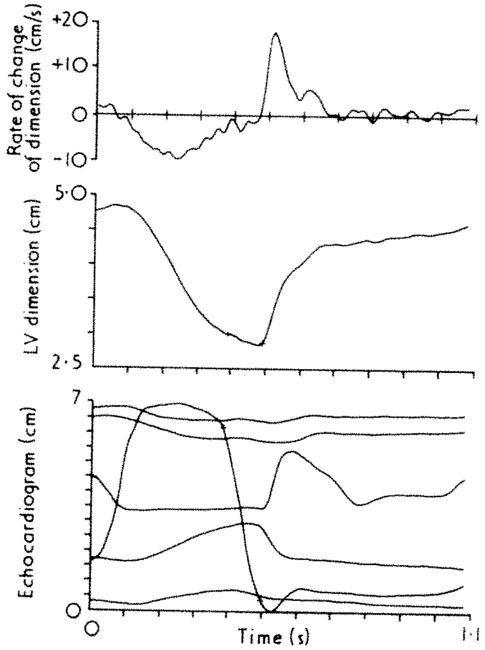

Fig. 4 *Digitised left ventricular echocardiogram from a normal subject, showing (from below) digitised data with superimposed apex cardiogram, left ventricular dimension, and (top) rate of change of dimension. The crosses represent the timing of aortic valve closure and mitral valve opening.*

and the filling period was prolonged to 295 ± 110 ms, significantly greater than normal (P < 0·01) (Fig. 6). It was not possible to differentiate between the three valve models present in the patients from the pattern of left ventricular wall movement.

Björk-Shiley prosthesis
The peak rate of increase of dimension was 10·5 ± 4·2 cm/s, significantly less than normal (P < 0·01) though greater than in the patients with a Starr-Edwards prosthesis (P < 0·001). The time to 20 per cent peak rate of increase was 180 ± 80 ms, which was not different from normal, though significantly less than in patients with a Starr-Edwards prosthesis (P < 0·001) (Fig. 7).

Hancock xenografts
The peak rate of increase of dimension was 10·3 ± 3·7 cm/s, similar to that in patients with a Bjørk-Shiley prosthesis though significantly less than normal (P < 0·01) and greater than in patients with a Starr-Edwards prosthesis (P< 0·05). In contrast to patients with a Björk-Shiley prosthesis, however, the time to 20 per cent peak rate was significantly prolonged to 245 ± 80 ms (P < 0·01 with respect to normal).

Mitral valve repair
In this group of patients, peak rate of increase of dimension and the time to 20 per cent peak rate were both normal (14·4 ± 5·0 cm/s and 170 ± 50 ms, respectively). In 20 of the 30 patients satisfactory measurements of peak diastolic closure rate were made; in them, this ranged from 50 to 240 m/s (mean 95 ± 60 mm/s), significantly lower than normal (mean 250 ± 60 mm/s) (P < 0·01). There was no relation in this group of patients between peak diastolic closure rate and the pattern of left ventricular wall movement and, in particular, a low mitral valve diastolic closure rate did not imply an abnormal pattern of increase of dimension during diastole (Fig. 8).

Postoperative mitral valve malfunction
In the 14 patients with a Starr-Edwards prosthesis and a paraprosthetic leak, peak rate of increase of

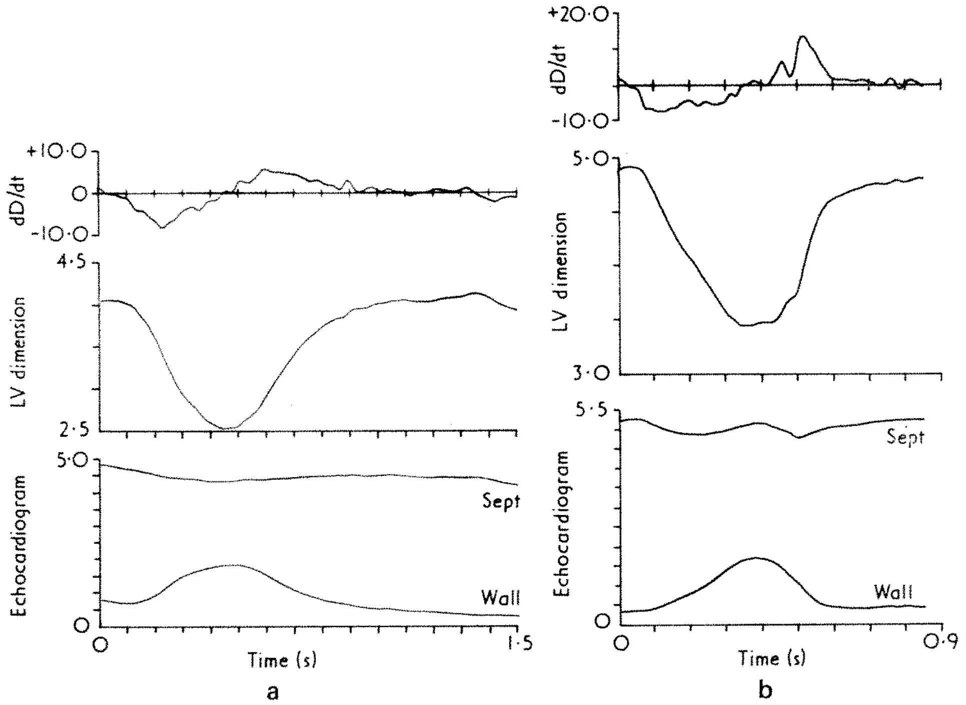

Fig. 5 (a) *Digitised left ventricular echocardiogram from a patient with mitral stenosis, showing (from below) septal and posterior wall echoes, transverse dimension, and (top) rate of change of dimension. Peak rate of change of dimension is reduced and the time to 20 per cent peak filling is prolonged.* (b) *Digitised echocardiogram from the same patient after closed mitral valvotomy.*

dimension was increased to 17·0 ± 2·0 cm/s, significantly higher than in patients with a normally functioning Starr-Edwards prosthesis ($P < 0{\cdot}01$), with almost no overlap between the two groups of patients. The time to 20 per cent peak filling rate, however, remained prolonged (240 ± 60 mm/s), presumably reflecting the increased stroke volume. In the 2 patients with a thrombosed Björk-Shiley prosthesis, the peak rate of increase of dimension was 4 and 5 cm/s and the filling time to 20 per cent was 230 ms. All these values are outside the 95 per cent confidence limits for the normally functioning valve.

Discussion

The present study has shown that, after successful mitral valve surgery, the pattern of left ventricular wall movement as assessed by M-mode echocardiography may be very abnormal. Peak rate of increase of left ventricular dimension is frequently reduced, the duration of filling prolonged, and septal movement reversed. The magnitude of these changes can be related to the surgical procedure undergone by the patient; the most abnormal values were recorded after Starr-Edwards replacement, whereas after mitral valve repair, the measurements were not significantly different from normal.

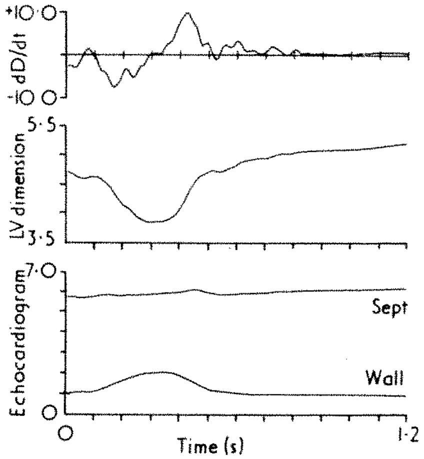

Fig. 7 *Digitised left ventricular echocardiogram from a patient with a mitral Bjork-Shiley prosthesis. Layout as Fig. 5.*

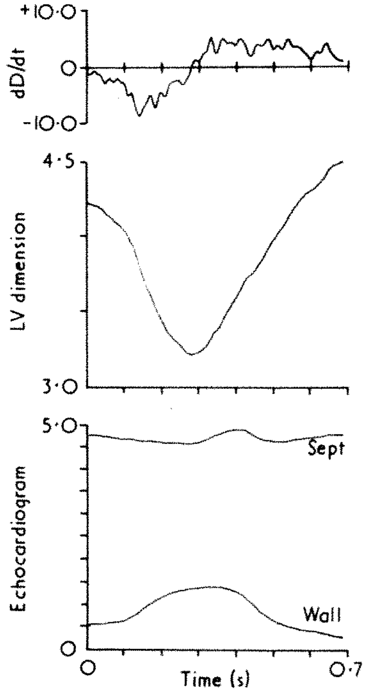

Fig. 6 *Digitised left ventricular echocardiogram from a patient with a mitral Starr-Edwards prosthesis. Layout as Fig. 5.*

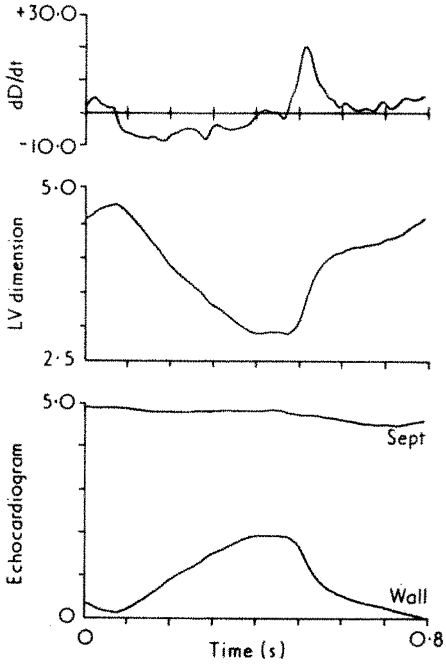

Fig. 8 *Left ventricular echocardiogram from a patient after mitral valve repair. Layout as Fig 5.*

In order to interpret these results, it was necessary to establish the relation between changes in a single ventricular dimension as measured by echocardiography and those in the cavity as a whole. This was most satisfactorily done using an angiocardiographic method in which the minor diameter was identified and compared with changes in cavity volume, estimated by the area length method (Sandler and Dodge, 1968). In this way, relatively close correlation between peak values of rate of change of dimension and those of volume was shown, a similar relation holding for normal subjects and patients with rheumatic mitral valve disease or mitral prosthesis, provided that the end diastolic dimension was less than 6 cm. This relation results from exclusion of patients in whom cavity size is very large, an unusual finding after mitral valve replacement, and reflecting the fact that changes in ventricular volume are mediated predominantly by alteration in minor axis (Lewis and Sandler, 1971). Comparison of the time relations between dimension and volume indicates that both the onset of increase and the time to 20 per cent peak value are the same in all patients studied, so that this method of assessing the filling pattern is independent of cavity size. Peak rate of increase of dimension was simultaneous with that of volume in patients with mitral stenosis or a mitral prosthesis, but preceded it by 20 ms in normal subjects, these results extending those previously reported (Prewitt *et al.*, 1975). There are, however, significant differences between echocardiographic and angiocardiographic measurements of left ventricular dimension. In particular, minimum angiographic dimension corresponds with end-ejection, and minimum echocardiographic dimension with the onset of mitral valve opening approximately 90 ms later. The exact basis of this discrepancy is not clear, but the difference almost exactly accounts for the apparent delay in the timing of peak rate of increase and 20 per cent peak rate of increase made by the two methods.

It has previously been shown that the diastolic pattern of left ventricular wall movement is abnormal in patients with mitral stenosis (Gibson and Brown, 1973). Not only is the peak rate of increase of dimension reduced, but there is also an increase in the interval from the onset of outward wall movement to the time when the rate of increase of dimension has fallen to 20 per cent of its peak value. The present angiographic results indicate that these changes reflect a corresponding reduction in peak left ventricular filling rate and an increase in filling time, both of which are characteristic of obstruction to the mitral valve orifice. This conclusion is strengthened by the increase in peak rate of increase of dimension and reduction in filling time occurring after successful mitral valvotomy.

In the present study, the lowest peak rates of increase of dimension were recorded after Starr-Edwards mitral replacement when filling time was prolonged to almost 300 ms, with a range of values overlapping that in patients with moderately severe mitral stenosis. In those patients with Björk-Shiley prostheses, peak rates of increase of dimension fell just on the lower limit of normal, and the filling time was within normal limits, this may result from the fact that the prosthesis has no central occluder and therefore a more laminar flow pattern. In patients with Hancock xenografts, peak rates of increase of dimension were virtually identical to those in patients with Björk-Shiley prostheses, though filling period was significantly longer. The only group of patients in whom both peak rate of wall movement and filling time were normal were those who had undergone mitral valve repair. The postoperative values of these two measurements in this last group were unrelated to whether the original mitral lesion was stenotic or regurgitant, or the underlying process rheumatic or degenerative, and in all the patients the peak rate of mid-diastolic mitral valve closure was strikingly reduced from normal values bearing no relation to peak rates of wall movement or filling time. This result is consistent with previous studies in patients with rheumatic mitral valve disease, showing that measurements of mitral diastolic closure rate are of little value in assessing the pattern of left ventricular filling (Gustafson, 1967; Winters *et al.*, 1969; Feigenbaum, 1972).

The present results are also consistent with haemodynamic assessments of mitral prostheses previously published. In general, mitral diastolic gradients at rest in patients with the models of Starr-Edwards prosthesis studied have been in the range 5 to 7 mmHg (Mason *et al.*, 1967; Morrow *et al.*, 1967; Glancy *et al.*, 1969; Kloster *et al.*, 1969; Russell *et al.*, 1972; Winter *et al.*, 1972; Rostad *et al.*, 1976). The present series did not contain any patients with size 2M prostheses, or model 6300, in whom mitral gradients are significantly higher (Glancy *et al.*, 1969; Kloster *et al.*, 1969; Reis *et al.*, 1970; Winter *et al.*, 1972). Diastolic gradients of 4 to 5 mmHg have been reported in patients with the mitral Björk-Shiley prosthesis 4 to 5 mmHg (Lepley *et al.*, 1973; Book, 1974; Rostad *et al.* 1976), and similar gradients have been observed in patients with Hancock valves (Horowitz *et al.*, 1974; Johnson *et al.*, 1975; McIntosh *et al.*, 1975). Though it is difficult to compare results in many different series, it appears that these haemodynamic studies are not incompatible with our findings.

Although differences in peak rates of wall movement and filling periods were clear cut, a number of factors must be considered before direct comparisons are made, either between any one type of prosthesis and rheumatic mitral valve disease, or between one prosthesis and another. Septal movement was reversed in all patients with a normally functioning Starr-Edwards prosthesis, and to a lesser extent, in those with Björk-Shiley prostheses. Though a previous angiographic study (Gibson and Brown, 1975) has shown that satisfactory estimates of peak rates of wall movement can be made in these circumstances, the presence of reversed septal movement strongly suggests that the pattern of left ventricular filling was abnormal. It is possible, therefore, that the relation between changes in dimension and in volume was altered in these patients in a manner which our studies did not define. Comparison with rheumatic valve disease on the basis of peak rates of wall movement alone may also be unsatisfactory, since this assumes that obstruction at the mitral valve orifice alone is responsible for the haemodynamic disturbance in rheumatic mitral stenosis. Recent studies have identified a group of patients in whom mitral gradients are low or absent and left ventricular end-diastolic pressure high in spite of severe symptoms, but in whom symptoms were relieved by mitral surgery, suggesting additional impairment of left ventricular filling by the subvalve apparatus (unpublished). It appears, therefore, that though these abnormalities of wall movement are related to the presence of a rigid mitral valve ring, an obstructed mitral orifice, and an abnormal flow pathway into the left ventricle, this relation is likely to be complex and indirect. At present, we prefer to regard them as consistent patterns rather than to link them directly to mitral diastolic gradients or flows.

Nevertheless, the range of peak rates of wall movement and filling times for the six groups of patients studied were so characteristic that departures from them could readily be recognised. This has obvious clinical value. In 14 patients with Starr-Edwards prostheses and silent para-prosthetic regurgitation, the peak rate of increase of left ventricular dimension was considerably increased, along with the reappearance of normal septal movement (Miller *et al.*, 1973; Burggraf and Craige, 1975). Two patients developed obstructed Bjørk-Shiley prostheses, resulting in a major reduction in peak rate of wall movement and prolongation of filling period, both of which returned to normal after successful reoperation. Two patients with mitral valve repair had low rates of wall movement postoperatively as a result of significant left ventricular inflow tract obstruction, and two had abnormally high peak filling rates suggesting that the repairs had been inadequate and had resulted in mitral reflux. These findings were also confirmed at a second operation.

The technique we have described thus seems to offer a simple, non-invasive means of assessing mitral valve function by examining the characteristics of left ventricular wall movement during filling. It can be used in the immediate postoperative period when cardiac catheterisation would be impracticable and hazardous. It makes possible early detection of valve malfunction, can be used to characterise available mechanical and biological prostheses, and gives information about left ventricular systolic function, particularly if combined with measurements of left ventricular pressure or apex cardiogram (Venco *et al.*, 1977). It may prove to be useful after conservative operations on the mitral valve when the haemodynamic characteristics of the result cannot be exactly predicted, so that a baseline for the assessment of progress can be established postoperatively in individual patients. Preliminary results suggest that it can provide the basis of physiological follow-up of the increasingly large population of patients who have undergone successful mitral valve surgery.

References

Book, K. (1974). Mitral valve replacement with Bjørk-Shiley tilting disc valve. *Scandinavian Journal of Thoracic and Cardiovascular Surgery*, Suppl 12, 1–28.

Braunwald, E., Braunwald, N. S., Ross, J., Jr., and Morrow, A. G. (1965). Effects of mitral valve replacement on the pulmonary vascular dynamics of patients with pulmonary hypertension. *New England Journal of Medicine*, **273**, 509–514.

Burggraf, G. W., and Craige, E. (1975). Echocardiographic studies of left ventricular wall motion and dimensions after valvular heart surgery. *American Journal of Cardiology*, **35**, 473–480.

Burr, L. H., Krayenbuhl, C. U., St. John Sutton, M. G., and Paneth, M. (1976). A new technique for mitral valve repair; early post-operative results. *Thorax*, **31**, 490.

Edler, I. (1967). Ultrasound cardiography in mitral valve stenosis. *American Journal of Cardiology*, **19**, 18–31.

Effert, S. (1967). Pre- and post-operative evaluation of mitral stenosis by ultrasound. *American Journal of Cardiology*, **19**, 59–65.

Feigenbaum, H. (1972): *Echocardiography*, p. 57. Lee and Feabiger, Philadelphia.

Feigenbaum, H., Linback, R. E., and Nasser, W. K. (1968). Hemodynamic studies before and after instrumental mitral commissurotomy. A reappraisal of the pathophysiology of mitral stenosis and the efficacy of mitral valvotomy. *Circulation*, **38**, 261–276.

Gibson, D., and Brown, D. J. (1973). Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *British Heart Journal*, **35**, 1141–1149.

Gibson, D., and Brown, D. J. (1975). Measurement of peak rates of left ventricular wall movement in man; comparison of echocardiography with angiography. *British Heart Journal,* **37,** 677–683.

Glancy, D., O'Brien, K. P., Reiss, R. L., Epstein, S. E., and Morrow, A. G. (1969): Hemodynamic studies in patients with 2m and 3m Starr-Edwards prostheses: evidence of obstruction to left atrial emptying. *Circulation,* **39–40,** Suppl. 1, 113–118.

Goodale, F., Sanchez, G., Friedlich, A. L., Scannell, J. G., and Myers, G. S. (1955). Correlation of pulmonary arteriolar resistance with pulmonary vascular changes in patients with mitral stenosis before and after valvulotomy. *New England Journal of Medicine,* **252,** 979–983.

Gustafson, A. (1967). Correlation between ultrasound cardiography, haemodynamics and surgical findings in mitral stenosis. *American Journal of Cardiology,* **19,** 32–41.

Horowitz, M. S., Goodman, D. J., Fogarty, T. J., and Harrison, T. C. (1974): Mitral valve replacement with the glutaraldehyde-preserved porcine heterograft. Clinical, hemodynamic and pathological correlations. *Journal of Thoracic and Cardiovascular Surgery,* **67,** 885–895.

Hultgren, H., Hubis, H., and Shumway, N. (1968). Cardiac function following mitral valve replacement. *American Heart Journal,* **75,** 302–312.

Johnson, A. D., Daily, O., Peterson, K. L., Le Winter, M., Di Donna, G. J., Blair, G., and Niwayama, G. (1975). Functional evaluation of the porcine heterograft in the mitral position. *Circulation,* **51–52,** Suppl. I, 40–47.

Johnson, M. L., Paton, B. C., and Holmes, J. H. (1970). Ultrasonic evaluation of prosthetic valve motion. *Circulation,* **41–42,** Suppl. 11-3–7.

Kloster, F. E., Herr, R. H., Starr, A., and Griswold, H. E. (1969). Hemodynamic evaluation of cloth-covered Starr-Edwards valve prosthesis. *Circulation,* **39–40,** Suppl. 1-119–125.

Lepley, D., Reuben, C. F., Flemma, R. J., Huston, J. H., Manley, J. C., Hoffman, J. F., and Tector, A. J. (1973). Experience with the Bjørk-Shiley prosthetic valve. *Circulation,* **47–48,** 111-51–55.

Lewis, R. P., and Sandler, M. (1971). Relationship between changes in left ventricular dimensions and the ejection fraction in man. *Circulation,* **44,** 548.

McIntosh, C. L., Michaelis, L. L., Morrow, A. G., Itscoitz, S. B., Redwood, D. R., and Epstein, S. E. (1975): Atrioventricular valve replacement with the Hancock porcine xenograft. A 5-year clinical experience. *Surgery,* **78,** 768–775.

Mason, D. T., Ross, J., Jr., Gault, J. H., Braunwald, E., and Morrow, A. G. (1967). Combined prosthetic replacement of mitral and aortic valves—preoperative and postoperative hemodynamic studies at rest, and the left ventricular response to muscular exercise. *Circulation,* **35–36,** Suppl. 1-15–23.

Miller, H. C., Gibson, D., and Stephens, J. (1973). Role of echocardiography and phonocardiography in the diagnosis of mitral paraprosthetic regurgitation with Starr-Edwards prostheses. *British Heart Journal,* **35,** 1217–1225.

Morrow, A. G., Oldham, H. N., Elkins, R. C., and Braunwald, E. (1967). Prosthetic replacement of the mitral valve: pre and post operative clinical and hemodynamic assessment in 100 patients. *Circulation,* **35,** 962–979.

Popp, R. L., and Carmichael, B. M. (1971). Cardiac echography in the diagnosis of prosthetic mitral valve malfunction (abstract). *Circulation,* **43–44,** Suppl. II, 33.

Prewitt, T., Gibson, D., Brown, D. J., and Sutton, G. (1975). The 'rapid filling wave' of the apexcardiogram: its relation to echocardiographic and cineangiographic measurements of ventricular filling. *British Heart Journal,* **37,** 1256–1262.

Reis, R. L., Glancy, D. L., O'Brien, K., Epstein, S. E., and Morrow, A. G. (1970). Clinical and hemodynamic assessments of fabric covered Starr-Edwards prosthetic valves. *Journal of Thoracic and Cardiovascular Surgery,* **59,** 84–91.

Rostad, H., Fjeld, N. B., and Hall, K. V. (1976). Experience with various types of mitral valve prostheses. *Scandinavian Journal of Thoracic and Cardiovascular Surgery,* **10,** 113–116.

Russell, T., II, Kremkau, E. L., Kloster, F. E., and Starr, A. (1972). Late hemodynamic function of cloth-covered Starr-Edwards valve prostheses. *Circulation,* **45–46,** Suppl. I, 8–13.

Sandler, H., and Dodge, H. T. (1968). The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *American Heart Journal,* **75,** 325–334.

Upton, M. T., Gibson, D. G., and Brown, D. J. (1976). Instantaneous mitral leaflet velocity and its relation to left ventricular wall movement in normal subjects. *British Heart Journal,* **38,** 51–58.

Venco, A., Gibson, D. G., and Brown, D. J. (1977). Relation between apexcardiogram and changes in left ventricular pressure and dimension. *British Heart Journal,* **39,** 117–125.

Winter, T. Q., Reis, R. L., Glancy, D. L., Robert , W. C., Epstein, S. E., and Morrow, A. G. (1972). Current status of the Starr-Edwards cloth-covered prosthetic cardiac valves. *Circulation,* **45–46,** 1–14–24.

Winters, W. L., Hafer, J., and Soloff, L. A. (1969). Abnormal mitral valve motion as demonstrated by the ultrasound technique in apparent pure mitral insufficiency. *American Heart Journal,* **77,** 196–205.

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Relation between phasic mitral flow and the echocardiogram of the mitral valve in man[1]

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Ten patients without valvular disease were studied by ventriculography, and the rate and pattern of phasic blood flow into the left ventricle were determined by ventricular volume determinations at intervals of 33 ms during a single diastolic filling period. The derived left ventricular inflow patterns were then compared with the echocardiographic mitral EF slope obtained no more than 25 minutes before left ventriculography. The steepness of the EF slope was found to be inversely correlated with the time required to reach peak inflow velocity ($r=0{\cdot}80$, $P<0{\cdot}01$) and directly correlated with the peak left ventricular inflow velocity divided by the time required to reach peak velocity ($r=0{\cdot}72$, $P<0{\cdot}05$). No correlation was found between mean flow velocity into the left ventricle and the EF slope ($r=0{\cdot}40$, $P=NS$). A significant inverse correlation was found between the EF slope and the fraction of the diastolic filling period elapsed when 50 per cent of the filling volume had entered the left ventricle ($r=-0{\cdot}85$, $P<0{\cdot}01$). These findings suggest that the time required to reach left ventricular peak inflow velocity is one of the determinants of the mitral EF slope.

The echocardiographic diastolic closure slope of the anterior mitral valve leaflet (EF slope) has become an important measurement in clinical cardiology. Several disorders of left ventricular function have been associated with lessening of the steepness of this slope in the absence of intrinsic mitral valve pathology (Schattenberg, 1968; Popp and Harrison, 1969; Shah *et al.*, 1971; McLaurin *et al.*, 1973), in particular abnormalities in the rate of left ventricular filling (Zaky *et al.*, 1968; DeMaria *et al.*, 1976) and left ventricular compliance (Quinones *et al.*, 1974). Though instantaneous mitral flow velocity throughout diastole has recently been measured in man (Kalmanson *et al.*, 1975a, b), the relation between the patterns of flow observed and echocardiographic motion of the anterior mitral leaflet was not examined. The present study was undertaken to examine this relation and define those levels of mitral flow important in determining the echocardiographic diastolic closure slope.

Methods

The study population consisted of 10 subjects (mean age 51 years) selected from a group of patients undergoing diagnostic left ventriculography and coronary cineangiography as part of an evaluation of chest pain thought to be angina pectoris. Patients with mitral and aortic valve disease and patients with intracardiac shunts were excluded. Patients were catheterised in the postabsorptive state after light sedation with oral diazepam. Intracardiac pressures were measured with Statham P23Db transducers. The zero pressure reference level was 5 cm posterior to the sternum with the patient supine. Left ventricular end-diastolic pressure was taken at a point 40 ms from the beginning of the QRS complex if a discrete A wave was not recorded. Before coronary angiography single plane left ventriculography was performed in the 30 degrees right anterior oblique projection using the brachial or femoral artery approach. Meglumine diatrizoate, 50 ml (Renografin 76), was injected into the cavity of the left ventricle at rates of 9 to 12 ml/s using a Viamonte-Hobbs power injector. The left ventriculograms were recorded at 60 frames/second on

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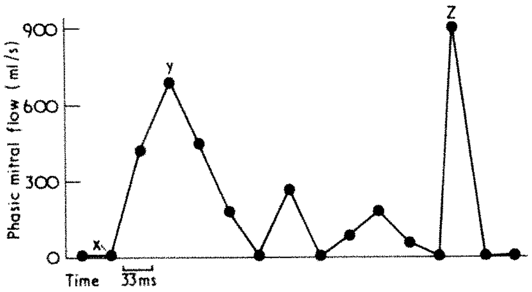

Fig. 1 *Graph of phasic mitral flow during diastole for case 3. The onset of left ventricular filling is marked by point X; initial peak inflow by point Y; late diastolic inflow associated with atrial contraction by point Z.*

35 mm film using either a Philips 6 in or a Siemens 7 in caesium iodide image intensifier. Correction factors for magnification and distortion were obtained for each patient using a standard 1 cm^2 angiocardiographic grid filmed at the level of the centre of the left ventricle (Dodge, 1971). The resolution of our cineangiocardiographic system was determined to be 3·7 line pairs per millimetre. Each ventriculogram was then viewed on a Vanguard XR-35 projector. Only those angiocardiograms with no ventricular irritability early in the injection were studied. A single complete diastolic filling period, usually the second or the third after the initiation of contrast medium injection, was then chosen for detailed analysis. The onset of diastole was identified by the ventriculographic frame first showing entrance of unopacified blood into the left ventricle. End diastole was identified by the frame with the greatest ventricular volume before the onset of left ventricular contraction. The ventricular outlines of alternate frames were traced throughot diastole. The outer margins of the ventricular silhouettes were defined by the outline of contrast medium between trabeculations. The papillary muscles were not excluded. The volume for every traced left ventricular silhouette was then calculated using the area-length method of Sandler and Dodge (1968) employing a computer assisted Graf-Pen system. The intraobserver reproducibility of the volume analysis was determined. Differences were found to be less than 1 per cent.

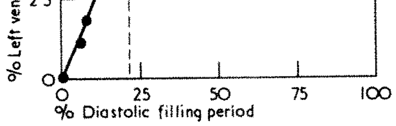

Fig. 2 *The percentage of left ventricular filling volume versus the percentage of diastolic filling period elapsed for case 3. Fifty per cent of the blood flow into the left ventricle has occurred during the first 22 per cent of the diastolic filling period.*

The ventriculographic stroke volume was taken as the difference between the end-diastolic and end-systolic volumes. Changes in ventricular volume between alternate cine frames of the diastolic filling period chosen for study were then determined. Since the time interval between alternate frames is 33 ms, the velocity of blood flow into the left ventricle was calculated for each 33 ms increment of the diastolic filling period and plotted as a function of time (Fig. 1). In this manner the pattern and rate of blood flow into the left ventricle could be graphically represented for each patient. From these plots the following values of diastolic left ventricular (LV) filling were calculated:

(a) mean LV inflow velocity (ml/s) =

$$\frac{\text{angiographic stroke volume}}{\text{diastolic filling period}}$$

(b) initial peak inflow velocity (ml/s) = point Y of Fig. 1

(c) time to the development of peak inflow velocity (s)

(d) $$\frac{\text{initial peak inflow velocity}}{\text{time to development of peak inflow velocity}}$$ (ml/s per s)

i.e. the slope of line X-Y (Fig. 1).

The pattern of blood flow into the left ventricle was displayed graphically in integral form by plotting the percentage of the diastolic filling time that had elapsed versus the percentage of total left ventricular filling that had been completed. For example, in case 3, 14 ml blood (i.e. 18% of the eventual filling volume) entered the left ventricular cavity by 33 ms (i.e. 8% of the eventual diastolic filling period). In like manner 46 per cent of the eventual filling volume entered the left ventricular cavity by 19 per cent of the eventual diastolic filling period, and so on. In this way the percentage of total diastolic flow into the left ventricle occurring with each 33 ms interval was plotted against the percentage of the total diastolic filling time elapsed (Fig. 2). Such graphs were plotted for each patient.

Table 1 *Basic haemodynamic and ventriculographic data for 10 study subjects*

Case No.	*Heart rate (beat/min)*		*LVEDP (mmHg)*	*LVEDV (ml)*	*SV (ml/beat)*	*Ejection fraction*	*CAD*	*Akinetic or dyskinetic LV wall motion abnormality*
	Angio	*Echo*						
1	74	88	25	387	120	0·31	1	Yes
2	60	68	6	105	58	0·55	2	0
3	67	65	6	138	80	0·58	1	0
4	71	70	5	157	110	0·70	2	0
5	53	60	2	48	32	0·67	0	0
6	66	64	5	126	88	0·70	1	0
7	53	62	18	198	119	0·60	3	Yes
8	54	66	5	120	53	0·44	2	Yes
9	62	65	6	168	123	0·73	0	0
10	62	72	6	151	112	0·74	1	0
Mean ±standard error	62·2 ±2·4	68 ±2·5	8 ±2	160 ±28	90 ±10	0·60 ±0·04		

LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; CAD, number of major coronary arteries with a 75 per cent or greater reduction in diameter; LV, left ventricle.

From these graphs the percentage of the diastolic filling time that had elapsed when 50 per cent of left ventricular filling had been completed could be identified for each patient.

Each patient underwent echocardiography in the supine position in the cardiac catheterisation laboratory no more than 25 minutes before left ventriculography. All echocardiograms were obtained with an Ekoline 20 Smith-Kline ultrasonoscope using 7·5 or 10 cm focused transducers held perpendicularly to the chest wall in the 3rd to 5th left intercostal spaces. Recordings of the anterior mitral valve leaflet were made with a Honeywell 1856 strip chart recorder at both 50 and 100 mm/s paper speed. Care was taken to record the mitral anterior cusp echo which had the maximal excursion and a monophasic diastolic closure slope (Rodger and Sumner, 1975). The diastolic closure slope (EF slope) of 10 consecutive beats was calculated and an average value obtained for each patient. The heart rate at the time of echocardiography was 6 beats/minute faster than at the time of left ventriculography.

The mitral valve EF slope was then compared with the ventriculographic measures of left ventricular filling using standard regression analysis (Keeping, 1962). Correlation coefficients were determined for each; a significant relation was considered to exist when $P < 0{\cdot}05$.

Results

The basic haemodynamic and ventriculographic data of the 10 patients studied are summarised in Table 1. Two patients had normal coronary arteries. Four had single vessel, 3 had double vessel and 1 had triple vessel coronary artery disease as manifested by a reduction in vessel diameter of 75 per cent or more. Three subjects had either akinetic or dyskinetic left ventricular wall segments. The left ventricular end-diastolic pressure and left ventricular end-diastolic volume ranged from 2 to 25 mmHg (mean 8 ±2 mmHg) and 48 to 387 ml (mean 160 ± 28 ml), respectively. The ejection fraction ranged from 0·31 to 0·74 (mean 0·60 ±0·04). There was no significant correlation between these haemodynamic measurements and the echocardiographic mitral EF slope.

Table 2 *Measures of diastolic LV inflow velocity*

Case No.	*EF slope (mm/s)*	*Mean flow velocity (ml/s)*	*Peak flow velocity (ml/s)*	*Time to peak flow (s)*	*XY slope (ml/s per s)*	*% of elapsed dfp at which 50 per cent flow has occurred*
1	109	520	780	0·149	5200	45
2	78	320	780	0·166	4700	46
3	198	190	690	0·066	10 400	22
4	165	220	570	0·099	5700	29
5	204	50	210	0·033	6300	17
6	130	190	420	0·133	3200	50
7	120	225	780	0·133	5900	26
8	85	80	210	0·099	2100	56
9	150	290	690	0·099	6900	33
10	110	260	510	0·099	5100	42
Mean ±standard error	135 ±14	230 ±40	565 ±70	0·108 ±0·013	5550 ±703	36·6 ±4·1

EF slope early diastolic closure slope of the anterior mitral valve leaflet echo; dfp, diastolic filling period; XY slope, slope of line between points X and Y on the phasic mitral flow plot, i.e. peak inflow velocity/time to peak inflow velocity in seconds.

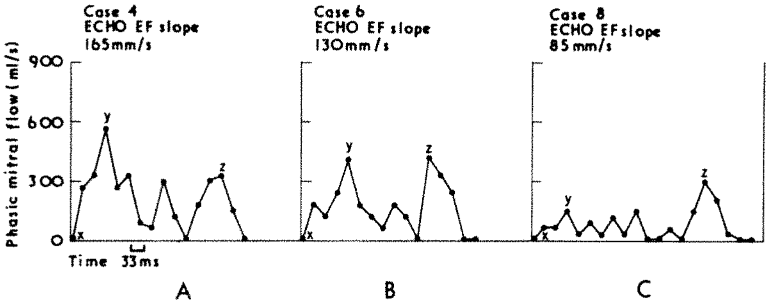

Fig. 3 *The patterns of phasic blood flow velocity into the left ventricle for 3 patients with differing echocardiographic mitral EF slopes. With the steeper EF slope the peak mitral inflow velocity (y) tends to be greater.*

Fig. 1 illustrates the pattern of blood flow into the left ventricle during diastole for case 3. With the opening of the mitral valve (X) the velocity of blood flow into the left ventricle increases rapidly until it peaks at (Y). After this point the inflow velocity falls off rapidly only to increase again with atrial contraction (Z).

The percentage of total diastole flow into the left ventricle against elapsed time expressed as a percentage of the diastolic filling period for case 3 is plotted in Fig. 2. Fifty per cent of the eventual blood flow into the left ventricle has occurred during the first 22 per cent of the total diastolic filling period.

Table 2 summarises the derived measures of the velocity of blood flow into the left ventricle in early diastole and the echocardiographic EF slope. The EF slope ranged from 78 to 204 mm/s with a mean of 135±14. The mean and initial peak blood flow velocity into the left ventricle were 230±40 ml/s and 70±70 ml/s, respectively.

Fig. 3A, B, and C illustrate the patterns of phasic blood flow velocity into the left ventricle for 3 of the patients with differing echocardiographic mitral valve EF slopes. With the steeper EF slope the peak mitral inflow velocity (Y) tends to be greater. Though the correlation between the EF slope and the initial peak inflow velocity did not reach statistical significance, there was a good negative correlation of the EF slope with the time required to reach peak flow velocity ($r=-0{\cdot}80$, $P<0{\cdot}01$) (Fig. 4). In addition there was a statistically significant correlation between the echocardiographic EF slope and initial peak inflow velocity divided by the time to the development of peak inflow velocity for each patient ($r=0{\cdot}72$, $P<0{\cdot}05$) (Fig. 5). There was no significant relation between the EF slope and the

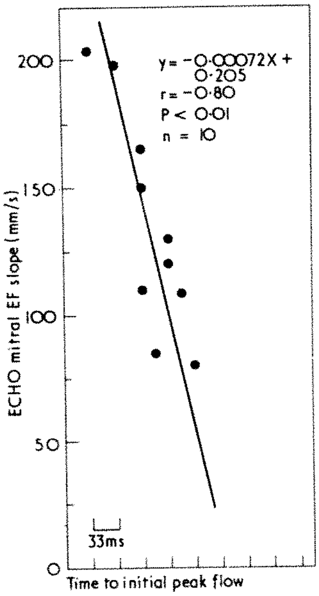

Fig. 4 *The echocardiographic EF slope versus the time required to reach peak inflow velocity.*

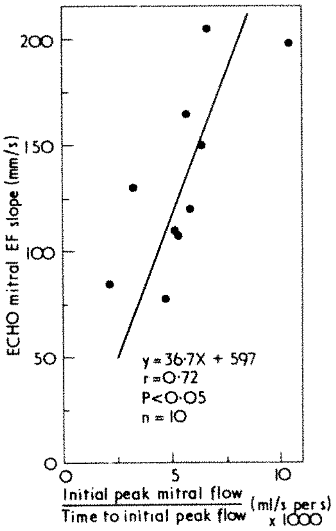

Fig. 5 *The echocardiographic EF slope versus the initial peak inflow velocity divided by the time to the development of peak inflow velocity.*

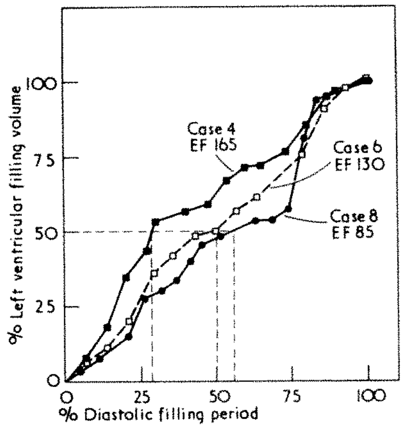

Fig. 6 *The percentage of left ventricular filling volume versus the percentage of the diastolic filling period elapsed for 3 patients with differing echocardiographic mitral EF slopes. With steeper EF slopes the curves are shifted to the left as a greater portion of the blood flow enters the ventricle earlier in diastole.*

overall mean velocity of blood flow into the left ventricle.

When the percentage of total diastolic flow occurring with each 33 ms increment of time is plotted against the percentage of the diastolic filling period elapsed for each patient, a series of curves is generated (Fig. 6). The curve is shifted to the left as a greater portion of the blood flow enters the ventricle earlier in diastole. For case 4 with an EF slope of 165 mm/s, 50 per cent of the left ventricular filling volume enters the ventricle during the initial 29 per cent of the diastolic filling period. For case 6 with an EF slope of 130 mm/s, 50 per cent flow has occurred by 50 per cent of the diastolic filling period. For case 8 with an EF slope of 85 mm/s, the 50 per cent flow point occurs at 56 per cent of the diastolic filling period. For the 10 study patients there was a statistically significant negative correlation between the echocardiographic EF slope and the percentage of the elapsed diastolic filling period at which 50 per cent flow occurred ($r = -0{\cdot}85$, $P < 0{\cdot}01$) (Fig. 7).

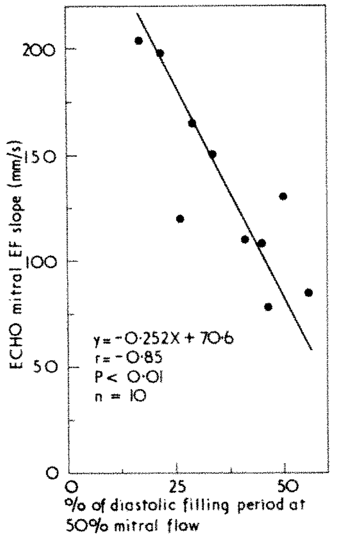

Fig. 7 *The echocardiographic EF slope versus the percentage of the elapsed diastolic filling period at which 50 per cent flow occurred.*

Discussion

Using standard ventriculographic and haemodynamic techniques we have derived the pattern of phasic left ventricular inflow velocity throughout diastole in selected patients with coronary artery disease and related the patterns derived to the echocardiographic motion of the anterior mitral valve leaflet. In these patients the echocardiographic EF slope was found to be significantly correlated with the time required to reach peak inflow velocity and with the initial peak left ventricular velocity divided by the time required to reach peak velocity, i.e. the rate of rise of flow velocity to peak inflow velocity. No correlation was found between overall mean flow velocity into the left ventricle and the EF slope. Finally, a significant negative correlation was found between the EF slope and the fraction of the diastolic filling period elapsed when 50 per cent of the filling volume had entered the left ventricle. These data suggest that the rate of early left ventricular filling, as manifested by the time required to reach initial peak inflow velocity, is one of the major determinants of the mitral EF slope.

Nolan *et al.* (1969) were among the first to examine the pattern of transmitral flow using electromagnetic flow transducers sewn to the left atrial wall of normal calves. Though they could distinguish 6 separate phases of diastolic transmitral flow they observed that left ventricular filling had two major components, a rapid passive early phase followed by an active late diastolic phase mediated by atrial contraction. More recently, Laniado *et al.* (1975), using a similar experimental model, reported a significant correlation between cardiac output and the echocardiographic mitral early diastolic closure slope in anaesthetised open chest dogs. The effect of changes in the rate of early diastolic filling on this slope was not examined directly. Kalmanson and colleagues have recently developed a technique for recording instantaneous mitral valve flow velocity in man by means of a directional Doppler ultrasound catheter positioned in the left atrium via the transseptal route (Kalmanson *et al.*, 1975a). Though the authors reported on the range of normal flow velocity patterns using this technique (Kalmanson *et al.*, 1975b) mitral valve echocardiograms were not examined.

In the present study, using standard ventriculographic techniques and equipment, phasic mitral valve flow was derived for each study subject and compared with the echocardiographic EF slope of the anterior leaflet of the mitral valve. The validity of such a frame-by-frame analysis of ventricular volumes to derive left ventricular phasic inflow velocity has been recently presented (Hammermeister *et al.*, 1974; Hammermeister and Warbasse, 1974). The patterns of left ventricular inflow derived using this method are quite similar to those previously observed, as mentioned above, in the experimental animal (Nolan *et al.*, 1969; Laniado *et al.*, 1975) and in man using the transseptal Doppler catheter (Kalmanson *et al.*, 1975a, b). Though the latter provides information only about the pattern of left ventricular inflow velocity and not flow volume (ml/s), the conversion of flow velocity to flow volume requires that the mitral orifice area be known throughout the diastolic filling period.

DeMaria and colleagues (1976) have recently examined the relation between the echocardiographic mitral diastolic closure slope and transmitral flow. By dividing diastole into three equal parts they were able to show a significant correlation between the EF slope and mitral flow during the initial third of diastole. The results of the present study confirm this finding. In addition we have extended the analysis by dividing diastole into 33 ms increments and by so doing have derived the pattern of phasic mitral flow for each study patient. Such an analysis has allowed us to determine that for patients with coronary artery disease the time required to reach peak inflow velocity may be a more important determinant of the steepness of the mitral EF slope than the peak inflow velocity itself.

The pattern of blood flow into the left ventricle was further analysed by determining the percentage of total left ventricular filling which had occurred for each cumulative increment in diastolic filling time. By plotting the percentage of the left ventricular filling volume which had entered the ventricle against the percentage of the diastolic filling period elapsed for each 33 ms study point throughout diastole a curve could be plotted for each patient. The curves of the patients with the steeper EF slopes were shifted to the left while those with the more attenuated slopes were shifted to the right. A significant negative correlation existed between the EF slope and the percentage of the diastolic filling period elapsed at 50 per cent flow.

It should be noted that such an analysis is based on the assumption that small differences in heart rate alone do not significantly alter the rate at which the left ventricle fills in early diastole. Though the validity of this assumption cannot be determined directly from our data, the lack of a correlation between heart rate and peak mitral flow, the time to peak mitral flow, and the rate of rise to peak flow in the present study indirectly support this assumption. In addition the range of heart rates observed in our study population during ventriculography is narrow. Any independent effect of these small differences in heart rate upon peak mitral flow, the time to the development of peak mitral flow, and the rate of rise to peak flow if present would be expected to be small.

Although it is frequently stated that differences in left ventricular compliance play an important role in determining the echocardiographic mitral diastolic closure slope (Shah *et al.*, 1969; Duchak *et al.*, 1972; Bergeron *et al.*, 1975), little direct evidence on this point is yet available. Layton *et al.* (1973) noted a significant relation while examining beat-to-beat variation in mechanically damped left ventricular end-diastolic pressure and simultaneously recorded mitral diastolic closure slope. Quinones *et al.* (1974) noted a significant correlation between the non-simultaneously recorded mitral EF slope and the calculated slope of the left ventricular log pressure-volume relation and the left ventricular end-diastolic distensibility index as derived from post a wave left ventricular end-diastolic pressure. The authors have correctly pointed out the potential limitations of such an approach (Quinones *et al.*, 1974; Gaasch *et al.*, 1975). DeMaria *et al.* (1976) were only able to show a general relation between the non-simultaneously recorded EF slope and total left ventricular diastolic compliance ($\Delta V/\Delta P$) normalised for end-diastolic volume. These investigators concluded that the mitral EF slope did not provide an accurate assessment of total left ventricular compliance in individual patients. In the present study measures of ventricular compliance were not examined. Such an investigation would require the examination of simultaneously recorded mitral EF slopes with measures of early, as well as total, diastolic compliance using high fidelity pressure recordings and simultaneous biplane angiographic volumes (Gaasch *et al.*, 1975)—techniques not available to us at the time of the study.

The subjects of the present study are a selected group of patients with varying degrees of coronary artery disease. Since patients with valvular heart disease were excluded and patients with congestive and hypertrophic cardiomyopathy were not studied the results of our analysis should not be extended to these disease states. Variation in vortex formation of the undersurface of the mitral leaflets and aberration in left ventricular geometry resulting in altered traction of papillary muscles on chordae tendineae may independently influence the echocardiographic mitral EF slope in these conditions (Madeira *et al.*, 1974).

In summary, using standard ventriculographic and haemodynamic techniques we have derived the pattern of phasic left ventricular inflow velocity throughout diastole in selected patients with coronary artery disease and related the patterns derived to the echocardiographic mitral valve diastolic closure slope. Our data suggest that the time required to reach mitral peak left ventricular inflow velocity is a significant determinant of the mitral EF slope. The reason for this relation is unclear but may be related in part to the earlier and more rapid development of vortices on the undersurface of the mitral leaflets resulting in more rapid early diastolic closure. The exact role and relative importance of altered left ventricular compliance in altering this relation requires further study using simultaneous high fidelity echocardiographic, haemodynamic, and ventriculographic measurements.

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References

Bergeron, G. A., Cohen, M. V., Teichholz, L. E., and Gorlin, R. (1975). Echocardiographic analysis of mitral valve motion after acute myocardial infarction. *Circulation*, **51**, 82–87.

DeMaria, A. N., Miller, R. R., Amsterdam, E. A., Markson, W., and Mason, D. T. (1976). Mitral valve early diastolic closing velocity in the echocardiogram; relation to sequential diastolic flow and ventricular compliance. *American Journal of Cardiology*, **37**, 693–707.

Dodge, H. T. (1971). Determination of left ventricular volume and mass. *Radiologic Clinics of North America*, **9**, 459–467.

Duchak, J. M., Jr., Chang, S., and Feigenbaum, H. (1972). The posterior mitral valve echo and the echocardiographic diagnosis of mitral stenosis. *American Journal of Cardiology*, **29**, 628–632.

Gaasch, W. H., Cole, J. S., Quinones, M. A., and Alexander, J. K. (1975). Dynamic determinants of left ventricular diastolic pressure-volume relations in man. *Circulation*, **51**, 317–323.

Hammermeister, K. E., Brooks, R. C., and Warbasse, J. R. (1974). The rate of change of left ventricular volume in man. I. Validation and peak systolic ejection rate in health and disease. *Circulation*, **49**, 729–738.

Hammermeister, K. E., and Warbasse, J. R. (1974). The rate of change of left ventricular volume in man. II. Diastolic events in health and disease. *Circulation*, **49**, 739–747.

Kalmanson, D., Bernier, A., Veyrat, C., Witchitz, S., Savier, C. H., and Chiche, P. (1975a). Normal pattern and physiological significance of mitral valve flow velocity recorded using transseptal directional Doppler ultrasound catheterization. *British Heart Journal*, **37**, 249–256.

Kalmanson, D., Veyrat, C., Bernier, A., Savier, C. H., Chiche, P., and Witchitz, S. (1975b). Diagnosis and evaluation of mitral valve disease using transseptal Doppler ultrasound catheterization. *British Heart Journal*, **37**, 257–271.

Keeping, E. S. (1962). *Introduction to Statistical Inference*. Van Nostrand, Princeton.

Laniado, S., Yellin, E., Kotler, M., Levy, L., Stadler, J., and Terdiman, R. (1975). A study of the dynamic relations between the mitral valve echogram and phasic mitral flow. *Circulation*, **51**, 104–113.

Layton, C., Gent, G., Pridie, R., McDonald, A., and Brigden, W. (1973). Diastolic closure rate of normal mitral valve. *British Heart Journal*, **35**, 1066–1074.

McLaurin, L. P., Gibson, T. C., Waider, W., Grossman, W., and Craige, E. (1973). An appraisal of mitral valve echocardiograms mimicking mitral stenosis in conditions with right ventricular overload. *Circulation*, **48**, 801–809.

Madeira, H. C., Ziady, G., Oakley, C. M., and Pridie, R. B. (1974). Echocardiographic assessment of left ventricular volume load. *British Heart Journal*, **36**, 1175–1181.

Nolan, S. P., Dixon, S. H., Fisher, R. D., and Morrow, A. G. (1969). The influence of atrial contraction and mitral valve mechanics on ventricular filling. *American Heart Journal*, **77**, 784–791.

Popp, R. L., and Harrison, D. C. (1969). Ultrasound in the diagnosis and evaluation of therapy of idiopathic hypertrophic subaortic stenosis. *Circulation*, **40**, 905–914.

Quinones, M. A., Gaasch, W. H., Waisser, E., and Alexander, J. K. (1974). Reduction in the rate of diastolic descent of the mitral valve echogram in patients with altered left ventricular diastolic pressure-volume relations. *Circulation*, **49**, 246–254.

Rodger, J. C., and Sumner, D. J. (1975). Measurement of diastolic closure rate of normal mitral valve. *British Heart Journal*, **37**, 504–513.

Sandler, H., and Dodge, H. T. (1968). The use of single plane angiocardiograms for the calculation of left ventricular volume in man. *American Heart Journal*, **75**, 325–334.

Shah, P. M., Gramiak, R., Adelman, A. G., and Wigel, E. D. (1971). Role of echocardiography in diagnostic and hemodynamic assessment of hypertrophic subaortic stenosis. *Circulation*, **44**, 891–898.

Shah, P. M., Gramiak, R., and Kramer, D. H. (1969). Ultrasound localization of left ventricular outflow obstruction in hypertrophic obstructive cardiomyopathy. *Circulation*, **40**, 3–11.

Schattenberg, T. T. (1968). Echocardiographic diagnosis of the left atrial myxoma. *Mayo Clinic Proceedings*, **43**, 620–627.

Zaky, A., Nasser, W. K., and Feigenbaum, H. (1968). A study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis. *Circulation*, **37**, 789–799.

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Echocardiography after reconstructive surgery for non-rheumatic mitral regurgitation[1]

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The echocardiographic appearances of the mitral valve after reconstructive surgery for non-rheumatic mitral regurgitation have been studied. Twenty-two patients, divided into 3 groups, were studied. In group 1 there were 12 patients with ruptured chordae tendineae and/or anterior mitral leaflet perforation, who underwent chordal reattachment and plication of leaflets or commissures. After operation common abnormalities were slow (<70 mm/s) diastolic EF slope (5 patients), multiple or dense echoes from valvular or subvalvular structures (5 patients), and abnormal posterior leaflet motion in diastole was observed in 3 patients. In group 2 there were 7 patients undergoing closure of an ostium primum atrial septal defect and primary repair by suture of a cleft anterior mitral leaflet. After operation slow EF slope occurred in 5 patients, but dense echoes were seen in only 1, and abnormal posterior leaflet echoes also in only 1. Group 3 consisted of 3 patients undergoing Carpentier ring insertion in the mitral annulus, all of whom showed dense echoes from the ring, with a slow EF slope in 2, and abnormal posterior leaflet motion in 2. Residual mitral regurgitation was common, as indicated by persistent mitral murmurs in 14. Systolic prolapse was not seen after operation. We conclude that echocardiographic abnormalities are common after reconstructive surgery for non-rheumatic mitral regurgitation. These abnormalities include multiple, dense valvular and subvalvular echoes, and abnormally slow and restricted diastolic motion of both leaflets suggesting that thickening, fibrosis, and decreased mobility of the valve apparatus occur because of the surgical plications and postoperative inflammatory changes. These structural changes were noted to be frequently accompanied by persistent mitral regurgitation.

The effect of operation on the mitral echogram has been evaluated previously, but such studies have concentrated on operations performed on rheumatic mitral valves (Mary *et al.*, 1973; Cope *et al.*, 1975), or on mitral replacement by various prostheses (Brodie *et al.*, 1976).

In mitral regurgitation of non-rheumatic origin, such as ruptured chordae tendineae caused by myxomatous degeneration or leaflet perforations secondary to bacterial endocarditis, mitral reconstructive surgery offers an alternative to valve replacement (Gerbode *et al.*, 1968; Selmonosky and Ehrenhaft, 1969; Manhas *et al.*, 1971). The ultrasonic appearances of the mitral valve after reconstructive procedures for non-rheumatic abnormalities have not been described in detail. The purpose of this study was to define the echocardiographic appearances after such mitral reconstructive surgery. We studied 3 groups of patients: patients with ruptured chordae tendineae and/or mitral leaflet perforation, patients with ostium primum atrial septal defect with a cleft anterior mitral leaflet, and patients undergoing Carpentier ring annuloplasty.

Methods

All patients at the University of Iowa and Iowa City Veterans Administration Hospitals who had undergone mitral reconstructive surgery for non-rheumatic mitral regurgitation were identified by reviewing the surgical files. Some were being followed regularly in our clinics; others were contacted and invited to return for re-examination. For this study 22 patients (12 men and 10 women) who underwent operation between August 1965 and October 1975 were re-examined. Their ages at time of surgery ranged from 13 to 66 years. All patients stated that they were improved after the operation and all were considered to be in functional class I or

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II (New York Heart Association) at the time of the examination.

All the patients were examined clinically and if a murmur was heard a phonocardiogram was recorded, using an Elema-Schonander 'mingograph' recorder. Echocardiograms were obtained using a Smith-Kline Ekoline ultrasonoscope and 2·25 mHz transducers, either unfocused or focused at 7·5 cm. Recordings were made on a Honeywell 1856 fibreoptic recorder. Recordings of the mitral valve were obtained using standard techniques (Feigenbaum, 1972). Standard measurements of left atrial dimension and left ventricular end-diastolic dimension (Feigenbaum, 1972) were made whenever the technical quality of the recordings permitted. The ventricular diameter was cubed to obtain left ventricular end-diastolic volume (Popp and Harrison, 1970; Pombo *et al.*, 1971). Since many of the patients had absent or paradoxical septal motion related to operation and/or volume overload, end-systolic volume or ejection fraction calculations would have been invalid. Measurements of the mitral valve diastolic closure velocity were made using the slope of the EF line. The normal EF slope in our laboratory is 70 to 150 mm/s. We also noted the presence or absence of multiple and/or dense valvular or subvalvular echoes, using normal sensitivity settings on the ultrasonoscope and attempting to relate density of the mitral echoes to those from the surrounding structures. The motion of the posterior leaflet of the mitral valve was considered abnormal if the leaflet failed to move posteriorly in early diastole (Duchak *et al.*, 1972).

Echocardiography was not routinely performed at the University of Iowa Hospital before 1971. Since many of our patients underwent reconstructive surgery earlier than this, preoperative echocardiograms were available for comparison in only 9 patients, and in 2 of these the records were from early studies using Polaroid photographs.

The patients were divided into 3 groups, depending on the type of operation. Group 1, consisting of 12 patients, had varying combinations of ruptured chordae tendineae to one or both mitral leaflets (9 patients), anterior leaflet perforation (4 patients), or papillary muscle dysfunction (1 patient). The aetiology of the chordal ruptures was considered to be myxomatous degeneration, while the perforations were the result of bacterial endocarditis. Operations on this group included varying combinations of reattachment of chordae (5 patients), plication of leaflets and/or commissures (10 patients), and pericardial patch or primary repair of perforations (3 patients). In group 2 the 7 patients all had ostium primum atrial septal defects with cleft anterior mitral leaflets. Operations in this group consisted of primary suture repair of the cleft leaflet plus pericardial or felt patch repair of the atrial septal defect. No chordal or other mitral apparatus operation was done in this group. Group 3 consisted of 3 patients: 1 with myxomatous degeneration of the mitral valve and 2 with papillary muscle dysfunction; all 3 underwent Carpentier ring annuloplasty. This is a procedure where a preformed, shaped ring is sewn into the mitral annulus in order to remodel the mitral valve, thereby reducing the annulus to its physiological dimensions and permitting better coaptation of the valve leaflets (Carpentier *et al.*, 1971). The mitral leaflets and suspensory apparatus were not directly operated upon in these 3 individuals.

Results

GROUP 1

The data from patients in group 1 are summarised in the Table. Of the 12 patients, 5 had preoperative echocardiograms. One showed systolic shuddering (Gramiak and Nanda, 1975) of the closed leaflet and 2 showed systolic prolapse (Fig. 1). One patient had a rapid EF slope (246 mm/s) and 1 had an EF slope below normal. Both patients in whom ventricular volumes could be calculated had large end-diastolic volumes (>160 ml).

After operation none of the patients had systolic prolapse or shuddering (Fig. 1). Abnormally strong or multiple echoes from valvular or subvalvular structures were present in 5 patients (Fig. 1 and 2). Posterior mitral leaflet motion in diastole was virtually absent in 3 patients (Fig. 1, 2, 3). The EF slope was rapid in 2 patients, normal in 5, and slow in 5. The mitral echogram appeared normal in 2 patients. The left ventricular volumes were large in 4 of the 6 patients in this group who had recordings adequate to calculate ventricular diameters. Four patients had an increased left atrial size ($>2·1$ cm/m^2). Of these 12 patients, 9 had persistent systolic murmurs (Fig. 4), including 1 of the 2 with a normal mitral echogram.

GROUP 2

The data from these patients also are summarised in the Table. Only 1 of these patients had a preoperative echocardiogram. After operation none had systolic prolapse, 5 of the 7 had slow EF slopes, and only 1 had abnormal posterior leaflet motion. Another had noticeably dense echoes from valvular and subvalvular structures (Fig. 5). Left ventricular volumes were enlarged in 2 of the 5 in whom this could be calculated. The left atrial size was increased in 3 patients. Five patients had persistent murmurs.

Table *Data of patients undergoing mitral valve reconstructive surgery*

Case No.	*Sex*	*Age (y)*	*Diagnosis at operation*	*Preop. mitral valve echo*				*Operation*	*Postop. mitral valve echo*						*Persistent MR murmurs*
				EF slope	*Prolapse*	*LAD*	*EDV*		*EF slope*	*Prolapse*	*Dense valvular or subvalvular echoes*	*Posterior leaflet motion*	*LAD*	*EDV*	
Group 1															
1	M	46	RCT-A and P	—	—	—	—	RA, P	58	None	Present	Normal	5·2	216	II/VI
2	F	30	ALP	—	—	—	—	CP, P	40	None	None	Abnormal	3·5	196	None
3	F	19	RCT-A and P	—	—	—	—	P	86	None	None	Normal	2·8	91	None
4	F	57	RCT-A, ALP	52	None	—	—	RA, P, CP	90	None	Present	Abnormal	—	—	III/VI
5	M	43	PMD	—	—	—	—	P	85	None	Present	Normal	3·7	220	IV/VI
6	M	37	RCT-A	150	None	—	—	RA, P	188	None	None	Normal	—	—	II/VI
7	M	45	RCT-P	—	—	—	—	RA	238	None	None	Normal	5·0	238	IV/VI
8	F	44	RCT-P	80	Present	—	—	P	72	None	Present	Abnormal	6·0	149	III/VI
9	M	54	RCT-P	246	Present	3·3	166	P	54	None	None	Normal	—	—	None
10	M	58	RCT-A	—	—	—	—	RA, P	40	None	None	Normal	—	—	II/VI
11	M	55	ALP, RCT-P	—	—	—	—	PP, P	74	None	None	Normal	4·0	—	I/VI
12	M	50	ALP	70	Shuddering	3·9	250	PP, CP	30	No shuddering	Present	Normal	3·0	—	I/VI
Group 2															
13	F	46	ASD, CAL	56	None	—	—	PD, S	62	None	None	Normal	3·1	—	II/VI
14	M	18	ASD, CAL	—	—	—	—	PD, S	80	None	None	Normal	2·6	125	II/VI
15	F	29	ASD, CAL	—	—	—	—	PD, S	62	None	None	Normal	2·7	—	None
16	F	63	ASD, CAL	—	—	—	—	PD, S	36	None	Present	Normal	5·7	227	V/VI
17	F	29	ASD, CAL	—	—	—	—	PD, S	58	None	None	Normal	5·0	110	II/VI
18	F	13	ASD, CAL	—	—	—	—	PD, S	80	None	None	Normal	2·2	64	None
19	M	16	ASD, CAL	—	—	—	—	PD, S	48	None	None	Abnormal	4·0	270	III/VI
Group 3															
20	F	66	MD	104	Present	5·3	118	CR	50	None	Present	Abnormal	5·3	196	None
21	M	62	PMD	128	None	5·3	314	CR	80	None	Present	Abnormal	4·8	275	None
22	M	64	PMD	125	None	—	—	CR	60	None	Present	Normal	4·0	—	None

Abbreviations

RCT, ruptured chordae tendineae supplying anterior (A) or posterior (P) leaflets; PMD, papillary muscle dysfunction; ALP, anterior leaflet perforation; ASD, atrial septal defect (ostium primum type); CAL, cleft anterior leaflet; RA, reattachment of chordae; P, plication of leaflets and/or commissures(s); CP, primary suture repair of perforation; PP, pericardial patch repair of perforation; PD, pericardial or felt patch repair of ASD; S, suture repair of leaflet cleft; MD, myxomatous degeneration of mitral valve; LAD, left atrial dimension; EDV, left ventricular end-diastolic volume; MR, mitral regurgitation; CR, Carpentier ring annuloplasty.

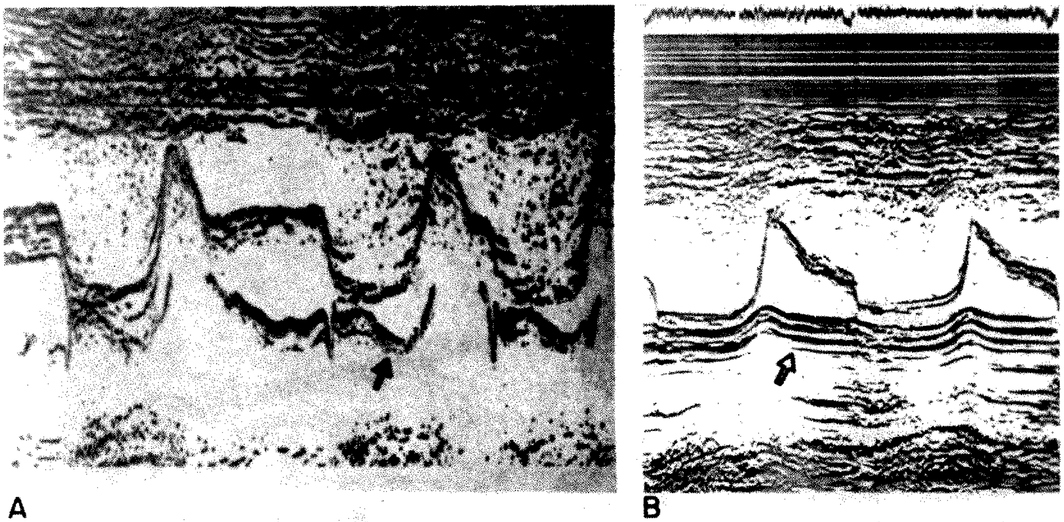

Fig. 1 *Echocardiograms from a patient with ruptured chordae tendineae and redundant posterior leaflet. (A) Preoperative echocardiogram, showing midsystolic mitral leaflet prolapse (closed arrow). (B) Postoperative echocardiogram, after posterior leaflet plication. Dense, multiple echoes from the posterior mitral leaflet (open arrow) are present, and the leaflet moves minimally in diastole. No prolapse is present.*

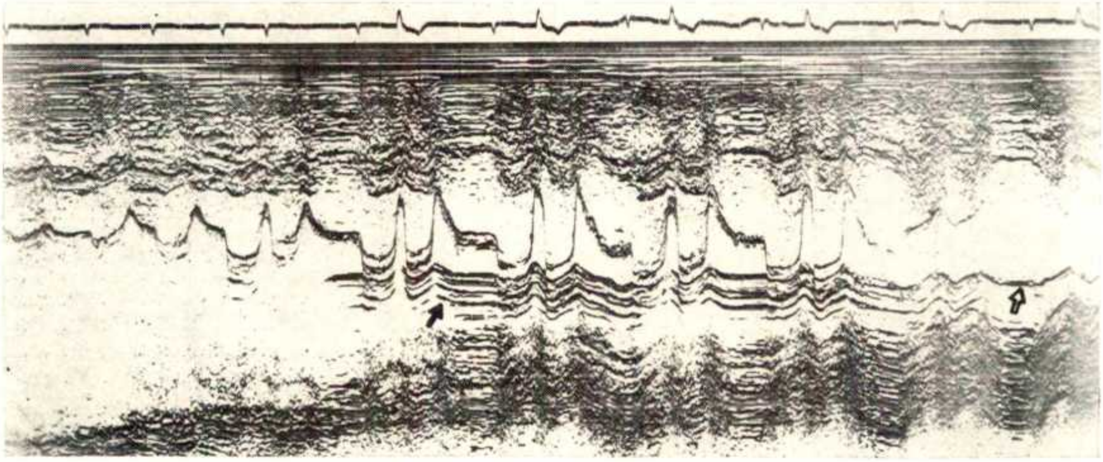

Fig. 2 *Postoperative echocardiographic sweep from the same patient as in Fig. 1. Dense, multiple echoes from the immobile posterior leaflet (closed arrow) are present. The echoes from the chordae tendineae (open arrow) are normal.*

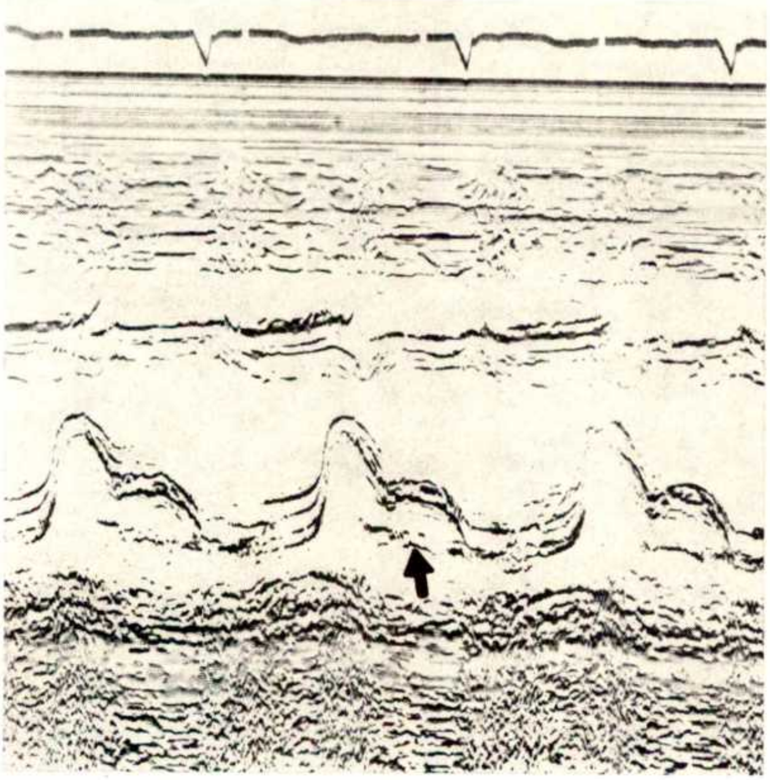

Fig. 3 *Postoperative echocardiogram from a patient who had had subacute bacterial endocarditis, ruptured chordae tendineae, and two anterior leaflet perforations. Operation consisted of reattachment of chordae, plication of the anterior commissure, and primary suture repair of the perforations. The motion of the posterior leaflet (arrow) is abnormal in diastole.*

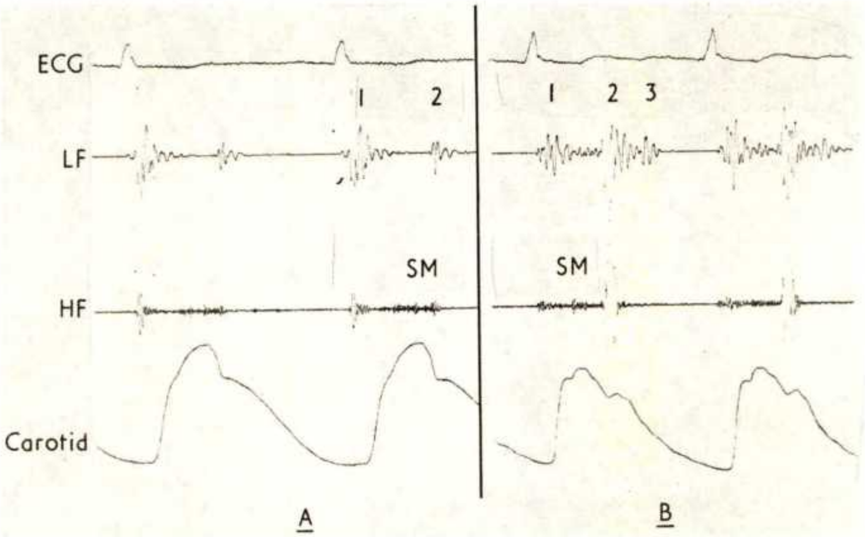

Fig. 4 *(A) Postoperative phonocardiogram from the patient shown in Fig. 1. A mid to late systolic murmur is present. (B) Postoperative phonocardiogram from the patient shown in Fig. 3. A holosystolic murmur and a third heart sound are present. Both recordings were made at the apical area. LF, low frequency band-pass filter; HF, high frequency filter; SM, systolic murmur.*

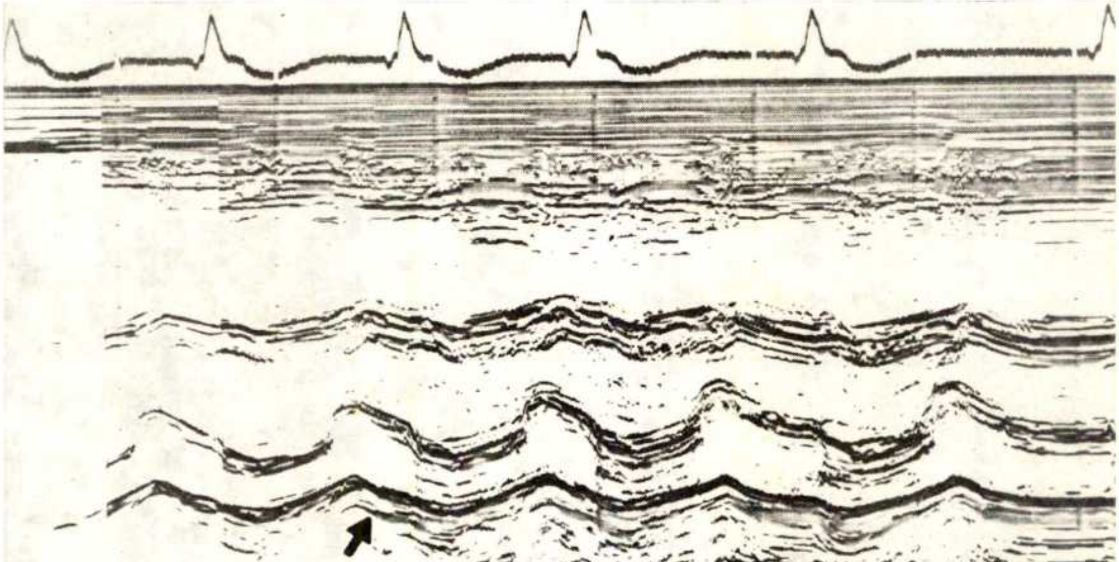

Fig. 5 *Postoperative echocardiogram from a patient with an ostium primum atrial septal defect and a cleft anterior mitral leaflet. Operation involved closure of the atrial septal defect and primary repair by suture of the cleft leaflet. The EF slope is slow, and there are dense, multiple echoes from the anterior mitral leaflet and the chordae tendineae (arrow).*

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GROUP 3

The data from these patients also are summarised in the Table. All 3 of these patients had preoperative echocardiograms, which showed normal EF slopes, prolapse in 1 patient, a large left atrium in 2 patients, and a large left ventricle in 1. After operation, new dense subvalvular echoes presumably from the prosthetic ring were recorded in all 3 patients (Fig. 6). The left atrium was enlarged in all 3 and the left ventricle in 2. The EF slopes became low in 2 of the 3 patients. None had postoperative murmurs.

Discussion

The most frequent postoperative echocardiographic abnormalities we encountered in patients undergoing mitral reconstructive procedures for nonrheumatic mitral regurgitation were combinations of multiple or dense echoes from valvular and subvalvular structures, abnormally restricted diastolic posterior leaflet motion, and reduced EF slope of the anterior leaflet. The strong, dense echoes are presumably the result of increased ultrasonic reflectance from leaflet and chordal structures which have been fused and thickened by suture and patch materials and by postoperative inflammatory changes. We graded as abnormal only those echoes that were noticeably stronger than adjacent echoes when the sensitivity settings of the ultrasonoscope were adjusted so that the left ventricle did not display an excessive number of intracavitary echoes. Thus, though the judgment of abnormally strong or multiple echoes is of necessity qualitative, we believe that these criteria are helpful in minimising the subjective aspects of this interpretation, and preventing overdiagnosis. Using similar methods the echocardiographic judgment of valvular thickening of fibrosis is commonly made in rheumatic mitral stenosis (Feigenbaum, 1972), and when vegetations of bacterial endocarditis are present (Roy *et al.*, 1976).

In the 7 patients with atrial septal defect who were undergoing repair of a cleft anterior leaflet, abnormally strong echoes were encountered after operation in only 1. This would be expected since this operation is less extensive than in the other two groups and should produce less thickening, fusion, and inflammation. Conversely, 5 of the 7 had slow diastolic motion of the anterior leaflet, which might be expected since this was the location of the repair (vide infra).

In the Carpentier ring patients the strong subvalvular echoes recorded are presumably from the mitral prosthetic ring itself. In position and appearance these echoes were similar to the dense echoes which have been noted in patients with mitral annular calcification (Hirschfeld and Emilson, 1975), where the calcium occupies an anatomical position analogous to the Carpentier ring.

Failure of the posterior mitral valve leaflet to open posteriorly in diastole was seen in 6 patients after operation. This presumably reflects restriction of normal leaflet motion caused by suturing of chordal and cuspal tissue and commissural plication (Selmonosky and Ehrenhaft, 1969) and possibly because of subsequent inflammatory changes as well. Similar posterior leaflet abnormalities are common in the immobile valve of mitral stenosis (Duchak *et al.*, 1972), but our patients did not have

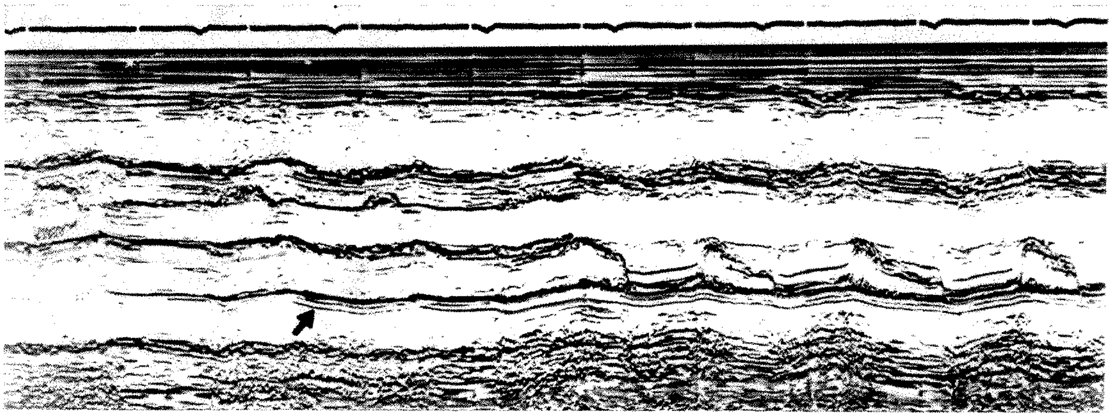

Fig. 6 *Postoperative echocardiographic sweep from a patient with papillary muscle dysfunction (coronary artery disease), after insertion of a Carpentier ring in the mitral annulus. Dense multiple echoes from the ring (arrow) are present and the posterior leaflet motion is abnormal in diastole.*

rheumatic disease and none had such abnormal posterior leaflet motion preoperatively.

A decreased EF slope—early diastolic closure velocity—was encountered postoperatively in 13 of these 22 patients, whereas this was seen in only 2 of the 9 available preoperative echoes. Several explanations for this are possible. Zaky *et al.* (1968) showed that the initial rate of descent of the anterior mitral leaflet (EFo slope) is primarily related to the early diastolic movement of the mitral ring; if there is a decreased rate of ventricular filling the mitral annulus will recede more slowly from the ultrasound transducer and hence the EF slope of the anterior leaflet mitral valve, determined by annular motion, would be reduced. Patients with reduced left ventricular compliance and hence slow ventricular filling would, therefore, be expected to have a decreased EF slope, and this is commonly seen in conditions such as aortic stenosis or hypertrophic obstructive cardiomyopathy (Duchak *et al.*, 1972; Popp and Harrison, 1969). Quinones *et al.* (1974), confirmed that a decreased mitral valve slope was associated with abnormalities of left ventricular diastolic pressure-volume relation. A decrease in the amount of mitral regurgitation because of operation should indeed reduce the rate of left ventricular filling, but only to the normal range. There is no *a priori* reason to suppose that operation would cause a chronic decreased rate of ventricular filling and low EF slope. In fact, 6 of the 12 patients with a low EF slope had residual mitral regurgitation, which would be expected to increase diastolic filling and result, if anything, in a rapid EF velocity. Thus, abnormally slow ventricular filling does not seem a likely explanation for the commonly encountered low EF slope in those patients.

Patients with mitral stenosis typically have slow EF slopes; this is the result of a combination of a thickened and immobile valve and slow ventricular filling caused by mitral obstruction (Zaky *et al.*, 1968). In the absence of rheumatic heart disease significant mitral orifice obstruction is not commonly produced by the type of reconstructive operation which our patients underwent (Selzer *et al.*, 1972), and none had diastolic rumbles audible or recordable after operation. However, postoperative cardiac catheterisation data are not available and we cannot entirely exclude the possibility that at least some degree of postoperative mitral obstruction was present in some patients. A more likely explanation, however, is that the low postoperative EF slope was the result of limitation of motion of the valve leaflet itself, resulting from the suturing and plication procedures which were done. The steeper part of the mitral diastolic descent (Fo-F slope) was the result of leaflet motion independent of annular movement (Zaky *et al.*, 1968); if this portion of the diastolic motion were reduced owing to partial leaflet immobilisation the net measured EF slope would be decreased.

Persistent regurgitant murmurs were present in 14 of our patients; previous investigators have also found a high incidence of postoperative murmurs in patients similar to ours (Manhas *et al.*, 1971; Selzer *et al.*, 1972). Systolic leaflet prolapse was not detected echocardiographically in any of our postoperative patients and thus prolapse cannot be a common cause of mitral regurgitation after reconstructive operations. Rather, the echocardiographic findings suggest that the postoperative regurgitation in these patients is caused by failure of the thickened and relatively immobile valve leaflets to coapt properly. In only 2 of the patients with murmurs was the mitral echogram entirely normal.

Left ventricular size was increased in 8 patients, 5 of whom had regurgitant murmurs. Left atrial size was increased in 9 patients, of whom 7 had murmurs. It seems likely that these high volumes were caused by significant mitral regurgitation.

We conclude that reconstructive operations for non-rheumatic mitral regurgitation frequently result in echocardiographic appearances suggestive of thickening, fibrosis, and decreased mobility of the valve apparatus, probably the result of a combination of surgical plications and postoperative inflammatory changes. These structural changes, rather than leaflet prolapse, are the likely cause of the persistent mitral regurgitation and left ventricular and atrial enlargement encountered in many patients undergoing this type of mitral operation. In addition to identifying the nature of the persistent valvular dysfunction in these individuals, this study should alert the echocardiographer to the possible confusion of these findings with the similar appearance of the rheumatic mitral valve. Exact information on the nature of previous mitral operations assists in the interpretation of postoperative echocardiograms.

References

Brodie, B. R., Grossman, W., McLaurin, L., Starek, P. J. K., and Craige, E. (1976). Diagnosis of prosthetic mitral valve malfunction with combined echo-phonocardiography. *Circulation*, **53**, 93–100.

Carpentier, A., Deloche, A., Dauptain, J., Soyer, R., Blondeau, P., Piwnica, A., and Dubost, C. (1971). A new reconstructive operation for correction of mitral and tricuspid insufficiency. *Journal of Thoracic and Cardiovascular Surgery*, **61**, 1–13.

Cope, G. D., Kisslo, J. A., Johnson, M. L., and Behar, V. S. (1975). A reassessment of the echocardiogram in mitral stenosis. *Circulation*, **52**, 664–670.

Duchak, J. M., Chang, S., and Feigenbaum, H. (1972). The posterior mitral valve echo and the echocardiographic diagnosis of mitral stenosis. *American Journal of Cardiology*, **29**, 628–632.

Feigenbaum, H. (1972). *Echocardiography*. Lea and Febiger, Philadelphia.

Gerbode, F., Hill, J. D., Kelly, J. J., Jr., Selzer, A., and Kerth, W. J. (1968). Surgical correction of mitral insufficiency due to ruptured chordae tendineae. *Circulation*, **37-38**, Suppl II, II-119–123.

Gramiak, R., Nanda, N. C. (1975). Mitral valve. In *Cardiac Ultrasound*, pp. 47–73. Ed. by R. Gramiak and R. C. Waag. Mosby, St. Louis.

Hirschfeld, D. S., and Emilson, B. B. (1975). Echocardiogram in calcified mitral anulus. *American Journal of Cardiology*, **36**, 354–356.

Manhas, D. R., Rittenhouse, E. A., Hessel, E. A., and Merendino, K. A. (1971). Reconstructive surgery for the treatment of mitral incompetence. *Journal of Thoracic and Cardiovascular Surgery*, **62**, 781–787.

Mary, D. A. S., Pakrashi, B. C., Wooler, G., and Ionescu, M. I. (1973). Study with reflected ultrasound of patients with mitral valve repair. *British Heart Journal*, **35**, 480–487.

Pombo, J. F., Troy, B. L., and Russell, R. O. (1971). Left ventricular volumes and ejection fraction by echocardiography. *Circulation*, **43**, 480–490.

Popp, R. L., and Harrison, D. C. (1969). Ultrasound in the diagnosis and evaluation of therapy of idiopathic hypertrophic subaortic stenosis. *Circulation*, **40**, 905–914.

Popp, R. L., and Harrison, D. C. (1970). Ultrasonic cardiac echography for determining stroke volume and valvular regurgitation. *Circulation*, **41**, 493–502.

Quinones, M. A., Gaasch, W. H., Waisser, E., and Alexander, J. K. (1974). Reduction in the rate of diastolic descent of the mitral valve echogram in patients with altered left ventricular diastolic pressure-volume relations. *Circulation*, **49**, 246–254.

Roy, P., Tajik, A. J., Giuliani, E. R., Schattenberg, T. T., Gau, G. T., and Frye, R. L. (1976). Spectrum of echocardiographic findings in bacterial endocarditis. *Circulation*, **53**, 474–482.

Selmonosky, C. A., and Ehrenhaft, J. L. (1969). The technique of open mitral reconstruction in the treatment of acquired and congenital mitral incompetence. *Journal of Cardiovascular Surgery*, **10**, 426–430.

Selzer, A., Kelly, J. J., Jr., Kerth, W. J., and Gerbode, F. (1972). Immediate and long-range results of valvuloplasty for mitral regurgitation due to ruptured chordae tendineae. *Circulation*, **45-46**, Suppl. I, I-52–56.

Zaky, A., Nasser, W. K., and Feigenbaum, H. (1968). A study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis. *Circulation*, **37**, 789–799.

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Plasma catecholamine levels and cardiac rhythm before and after cardiac catheterisation

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Plasma catecholamine concentrations were estimated in a group of 17 fasting patients immediately before and 3 days after cardiac catheterisation. At both times electrocardiograms were recorded and blood pressures, heart rates, and respiration rates measured. Control catecholamine values were established in a group of 10 male and 10 female volunteers, bled at the same time of day under the same conditions of nutrition and posture. Levels of adrenaline and noradrenaline were increased substantially before catheterisation; 3 days later, the values were comparable to those of the control group, though still marginally higher. The increments in catecholamine levels were independent of sex and of the presence or otherwise of persistent supraventricular arrhythmias. In spite of the considerably raised catecholamine levels, electrocardiographic patterns remained unchanged, as did the other physiological values. The absence of any relation between enhanced catecholamine secretion and physiological effects is considered to be the result either of enhanced parasympathetic activity or of adaptation to a prolonged period of stress.

The close links between the sympathoadrenal system and the metabolic consequences of stress have been exemplified by the increased catecholamine excretions observed under different conditions, including apprehension and uncertainty (von Euler, 1964; Frankenhaeuser and Rissler, 1970; Levi, 1970; Konzett *et al.*, 1971; Myager, 1971). Furthermore, in recent years, increased concentrations of plasma catecholamines have been reported during the stressful period immediately after an acute myocardial infarction and attempts have been made to relate these raised levels to the simultaneous presence of cardiac arrhythmias (McDonald *et al.*, 1969; Nelson, 1970; Griffiths and Leung, 1971; Siggers *et al.*, 1971; Lukomsky and Oganov, 1972). The results of these studies have been conflicting or equivocal.

In such circumstances it is possible that evidence for a direct relation between cause and effect was masked by the consequences of either the clinical event or the selective therapy necessarily administered to the patient. These considerations prompted investigation of the possible effects of increased plasma catecholamine concentrations upon cardiac rhythm in subjects who had not suffered a myocardial infarction. This paper describes such a study in a group of patients about to undergo cardiac catheterisation, who had been in an increasingly anxious state for some days. Previous investigations of the interrelation between stress and arrhythmia promotion in subjects free from acute clinical conditions has been confined to short-term stress situations (Carlson *et al.*, 1968; Taggart *et al.*, 1972, 1973).

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Subjects and methods

SUBJECTS

The group studied, all of whom had given their informed consent, comprised 17 patients, 6 of whom were male; the mean age was 42 ± 14 years. Fourteen subjects had evidence of mitral and/or aortic valve disease and 3 had septal defects (Table 1). None had hepatic, hormonal, renal, or gastrointestinal disorders, and none was receiving drugs or foodstuffs known to influence the metabolism or the estimation of catecholamines.

In addition, control levels of the amines were established in a group of 10 male and 10 female staff members, none of whom was apprehensive of venepuncture. Their mean age was 34 ± 7 years.

PROCEDURE

The patients were admitted to hospital one week before investigation, ate a normal diet, and were allowed light physical activity. Before catheterisation, each subject fasted overnight and immediately before premedication, at 0830 h, blood was withdrawn with minimal stasis from the antecubital fossa while resting in a supine position. At the same time, a 60-second bipolar limb lead electrocardiogram was recorded, and blood pressure, heart rate, and respiration rate were measured. Three days later, when the patients had recovered from the catheter investigation and were more relaxed, the procedure was repeated identically.

After an overnight fast, each member of the control group was bled from the same site at the same time of day, 0830 h, after resting in the supine position for at least 15 minutes.

ANALYSES

All specimens (20 ml) were collected in precooled glass bottles, containing EDTA (20 mg) as anticoagulant and cooled immediately in ice. After centrifugation at 4°C, plasma was removed and deproteinised by the addition of one-tenth volume of 4M perchloric acid. The supernatant obtained on further centrifugation was stored at −18°C before analysis. Details of the method for catecholamine separation using Dowex ion exchange resin and subsequent assay by differential spectrophotofluorimetry have been reported previously (Turton and Deegan, 1973).

STATISTICS

All results are expressed as mean ± standard deviation; data were analysed by the appropriate Student's t tests with a 5 per cent level of significance.

Table 1 *Clinical data*

Case No.	*Sex*	*Age (y)*	*Diagnosis*	*Rhythm*
1	F	16	Ventricular septal defect	Sinus
2	F	64	Atrial septal defect	Sinus
3	F	27	Mitral regurgitation	Sinus
4	M	56	Mitral stenosis	Sinus
5	F	52	Mitral stenosis	Sinus
6	M	28	Aortic stenosis and regurgitation	Sinus
7	M	45	Aortic stenosis and regurgitation	Sinus
8	M	37	Mitral stenosis	Sinus
9	M	58	Aortic stenosis	Sinus
10	M	19	Atrial septal defect	Atrial flutter
11	F	42	Mitral stenosis and regurgitation	Wandering pacemaker
12	F	55	Mitral stenosis	Atrial fibrillation
13	F	40	Mitral stenosis, aortic and tricuspid regurgitation	Atrial fibrillation
14	F	45	Aortic regurgitation; mitral stenosis and regurgitation	Atrial fibrillation
15	F	38	Mitral stenosis	Atrial fibrillation (DK)
16	F	47	Tricuspid and mitral stenosis; mitral regurgitation	Atrial fibrillation (DK)
17	F	46	Mitral stenosis	Atrial fibrillation (DK)

(DK): associated with digoxin and/or hypokalaemia.

Results

CATECHOLAMINES

The mean plasma concentrations of both catecholamines before catheterisation were higher than those recorded 3 days later ($P<0{\cdot}001$, both amines; Table 2). Analyses of the significances of the differences between pairs of individual values supported these findings ($P<0{\cdot}001$, both amines). The precatheterisation mean values were also much higher than the corresponding control mean concentrations ($P<0{\cdot}001$, both amines; Table 2) and only 3 patients had levels of both catecholamines below the upper limits of normality of 1·6 nmol/l for adrenaline and 3·4 nmol/l for noradrenaline, based upon the respective control mean values +2 SD. Though the postcatheterisation mean values were also higher than the corresponding control values (Table 2), the differences were not significant. Nevertheless, 6 patients still had one or both catecholamine concentrations greater than the respective upper limits of normality.

Male and female patients reacted equally to the stressful situation before catheterisation and had similar mean levels of both catecholamines 3 days later. Though women showed bigger differences between the mean values of the two amines before and after catheterisation, neither effect was significant because of the wide ranges of the differences between pairs of individual values, which resulted in large associated standard deviations for both sexes (Table 2).

The electrocardiograms showed that 9 patients were in sinus rhythm throughout the study. Of

Table 2 *Mean levels of plasma catecholamines before and after cardiac catheterisation (nmol/l)*

Subjects	*n*	*Time*	*Adrenaline*	*Noradrenaline*
All patients	17	Before	4·2 ±2·6	6·8 ±3·1
		After	1·2 ±0·8	2·6 ±1·4
		Difference	3·0 ±2·3	4·2 ±3·4
Males	6	Before	3·8 ±2·6	6·4 ±3·3
		After	1·3 ±0·9	3·0 ±2·0
		Difference	2·5 ±2·2	3·4 ±4·3
Females	11	Before	4·4 ±2·8	7·0 ±3·1
		After	1·2 ±0·9	2·4 ±1·0
		Difference	3·2 ±2·5	4·6 ±3·0
Arrhythmias	8	Before	3·6 ±1·9	6·1 ±2·8
		After	1·3 ±0·8	3·1 ±1·6
		Difference	2·2 ±2·2	3·0 ±3·6
Sinus rhythm	9	Before	4·7 ±3·2	7·3 ±3·4
		After	1·1 ±0·9	2·2 ±1·0
		Difference	3·6 ±2·4	5·1 ±3·1
Normals	20		0·8 ±0·4	1·8 ±0·8
Males	10		0·9 ±0·5	1·8 ±0·7
Females	10		0·8 ±0·4	1·6 ±0·8

the rest, 1 patient had atrial flutter, 1 a wandering pacemaker, and 6 were in atrial fibrillation, 3 of whom had RS-T-T wave changes associated with either digitalis therapy or hypokalaemia or both (Table 1). The 8 supraventricular arrhythmias of moderate severity were present in the same form and to the same degree at both times of investigation. No differences were detected between the mean values for either catecholamine in those patients who had arrhythmias and those who were in sinus rhythm, either before or after catheterisation. The apparently larger responses to stress seen in the patients in sinus rhythm were not significant because of the wide ranges of the differences between pairs of individual values, in like manner to the comparable effect in the responses of the male and female patients (Table 2).

PHYSIOLOGICAL DATA

The mean values for heart rate, respiration rate, and mean diastolic blood pressure before and after catheterisation were almost identical (Table 3) and no significant findings emerged from analyses of the significances of the differences between pairs of individual values in any factor. The physiological data were also independent of the sex of the patients and of the presence or absence of supraventricular arrhythmias.

Discussion

In common with other stressful conditions, the period of apprehension preceding cardiac catheterisation was accompanied by increased catecholamine secretion. Plasma concentrations of both adrenaline and noradrenaline were raised considerably with respect to control values established in normal resting volunteers, bled at a similar time of day, and under the same conditions of nutrition and posture. Three days after catheterisation, when the stimulus had disappeared and the patients were less apprehensive, the mean levels of both catecholamines in the two groups were comparable, though the values for the patients were the higher in both cases, and individually, in 6 of the group, exceeded the upper limits of normality for one or both amines. Similar slight increases in mean catecholamine concentrations were also observed in another group of patients admitted for cardiac catheterisation, when they were investigated just before leaving hospital (Turton and Deegan, 1974). Collectively, these findings suggest that admission to hospital *per se* induces some increase in catecholamine secretion and that allowance should be made for this effect in any investigations of in-patients.

Table 3 *Mean values of physiological data in patients before and after cardiac catheterisation*

Subjects	*n*	*Time*	*HR**	*RR**	*MDP**
All patients	17	Before	82 ±11	22 ±4	98 ±9
		After	86 ±11	22 ±3	101 ±7
		Difference	−4 ±11	0 ±4	−4 ±7
Males	6	Before	81 ±7	21 ±4	95 ±10
		After	81 ±6	23 ±3	98 ±6
		Difference	0 ±10	−2 ±3	−2 ±5
Females	11	Before	81 ±13	23 ±6	98 ±9
		After	89 ±11	21 ±3	103 ±8
		Difference	−7 ±11	1 ±5	−5 ±9
Arrhythmias	8	Before	82 ±13	21 ±5	100 ±10
		After	84 ±13	21 ±4	104 ±5
		Difference	−2 ±13	0 ±4	−4 ±9
Sinus rhythm	9	Before	81 ±9	22 ±6	94 ±8
		After	88 ±6	22 ±3	98 ±8
		Difference	−7 ±9	1 ±5	−4 ±7

*HR, heart rate (per min); RR, respiration rate (per min); MDP, mean diastolic pressure (mmHg).

Men and women reacted equally to the stress stimulus and no sex-based differential existed in the levels afterwards or in those of the control group. Previous reports on this aspect have been conflicting; whereas Engelman *et al.* (1970) found identical responses in male and female members of a group of hypertensive patients, de Quattro and Chan (1972) found higher levels of catecholamines in women in a similar group. However, in both studies, comparable levels were recorded in both sexes in the normal subjects. Throughout the present study, 8 patients had supraventricular arrhythmias. No influence upon plasma catecholamine levels resulting from these persistent abnormalities was observed at any time.

The increased adrenaline and noradrenaline concentrations were not accompanied by any significant changes in mean diastolic pressures, heart rates, or respiration rates. In contrast, when Carlson *et al.* (1968) exposed subjects intermittently, for periods of 2 hours, to standardised emotional stress of moderate degree, consisting of intense mental activity while being disturbed by flashing lights and noise, increases in heart rate were observed. On the other hand, no increases of systolic or diastolic pressure were detected.

The increased levels of catecholamines before catheterisation were not accompanied by the genesis of cardiac arrhythmias or the modification of the supraventricular arrhythmias. The latter were present in the same form and in the same frequency at a time which may be regarded as a control period, 3 days after the catheter investigation. These observations conflict with reports of electrocardiographic abnormalities and of the occurrence of multiple ectopic beats, concomitant with the stress reactions to the intense moist heat of a sauna bath (Taggart *et al.*, 1972) and to public speaking (Taggart *et al.*, 1973), seen in both normal subjects and subjects with coronary artery disease. Under the former conditions, a group of 9 subjects with coronary artery disease had increased heart rates and ST-T segment abnormalities, in the presence of levels of adrenaline (3·8 ± 2·6 nmol/l) and noradrenaline (5·4 ± 2·0 nmol/l) comparable to those found before catheterisation in the present study. Ventricular ectopic beats were also detected in 4 out of 17 normal subjects, whose mean adrenaline and noradrenaline levels were 1·6 ± 0·9 nmol/l and 3·6 ± 0·8 nmol/l, respectively. Separate information on the values in the subjects in whom arrhythmias were observed was not provided. Increased heart rates and electrocardiographic abnormalities were also evident in a group of 23 normal subjects and in a group of 7 subjects with coronary artery disease, when speaking before an audience. In addition, unspecified increments in plasma noradrenaline levels were reported in 21 normal subjects, when monitored immediately after speaking.

The absence of changes in heart rate and electrocardiographic pattern in the present study is possibly the result of the slower development of the apprehensive state, which produced a more controlled response in catecholamine secretion throughout a longer period than that in the conditions imposed by Carlson *et al.* (1968) or in either taking a sauna bath (Taggart *et al.*, 1972) or public speaking (Taggart *et al.*, 1973). The relative suddenness of the responses to the latter events produced changes in heart rate, which were not observed under the more gradual conditions of the former. Since, within the limitations of the different techniques used and the incompleteness of the data in some respects, increased catecholamine secretion was a common feature of all the studies, it appears that electrocardiographic abnormalities were more prone to develop when such increased secretion was accompanied by changes in heart rate.

The failure of high adrenaline levels to induce increased heart rates may parallel the observation of Taggart *et al.* (1976), who reported bradycardia in the presence of increased circulating adrenaline in a group of young women undergoing dental surgery. It was suggested that, in this situation, parasympathetic responses evoked by pain or the expectation of pain predominated over sympathetic responses which would tend to increase the heart rate. Some support for this concept is provided by the physiological data in the present study. Though no significant differences were found between the mean values for heart rate, respiration rate, and mean diastolic pressure before and after catheterisation, 9 of the group had decreased heart rates and 10 had decreased mean diastolic pressures before catheterisation compared with the values afterwards. In addition, at the latter time, when any expectation of pain was absent, the values recorded were consistent with mild sympathetic responses to the concurrent marginal increases in catecholamine secretion.

Alternatively, the overall absence of any physiological responses to raised catecholamine levels may reflect the general adaptation syndrome described by Selye (1946) and may involve a process whereby the secondary effects promoted by a primary increase in plasma concentrations gradually disappear as the subject adapts to the modified situation. Such a view would be consistent with the more prolonged period of stress involved, compared with those of the investigations previously described.

References

Carlson, L. A., Levi, L., and Crö, L. (1968). Plasma lipids and urinary excretion of catecholamines in man during experimentally induced emotional stress, and their modification by nicotinic acid. *Journal of Clinical Investigation*, **47**, 1795–1805.

de Quattro, V., and Chan, S. (1972). Raised plasma catecholamines in some patients with primary hypertension. *Lancet*, **1**, 806–809.

Engelman, K., Portnoy, B., and Sjoerdsma, A. (1970). Plasma catecholamine in patients with hypertension. *Circulation Research*, **26-27**, Suppl. 1, 141–145.

Frankenhaeuser, M., and Rissler, A. (1970). Catecholamine output during relaxation and anticipation. *Perceptual and Motor Skills*, **30**, 745–746.

Griffiths, J. C., and Leung, F. (1971). The sequential estimation of plasma catecholamines and whole blood histamine in myocardial infarction. *American Heart Journal*, **82**, 171–179.

Konzett, H., Hörtnagl, H., Hörtnagl, H., and Winkler, H. (1971). On the urinary output of vasopressin, epinephrine and norepinephrine during different stress situations. *Psychopharmacologia*, **21**, 247–256.

Levi, L. (1970). Emotional stress and sympathoadrenomedullary and related physiological reactions with particular reference to cardiovascular pathology. In *Psychosomatics in Essential Hypertension*, p. 38. (Bibliotheca Psychiatrica, No. 144.) Ed. by M. Koster, H. Musaph, and P. Visser. Karger, Basel.

Lukomsky, P. E., and Oganov, R. (1972). Blood plasma catecholamines and their urinary excretion in patients with acute myocardial infarction. *American Heart Journal*, **83**, 182–188.

McDonald, L., Baker, C., Bray, C., McDonald, A., and Restieaux, N. (1969). Plasma catecholamines after cardiac infarction. *Lancet*, **2**, 1021–1023.

Myager, V. (1971). Psychic trauma and cortical-diencephalic interrelationships. In *Society, Stress and Disease*, vol. 1, p. 258. Ed. by L. Levi. Oxford University Press, London.

Nelson, P. G. (1970). The effect of heparin on serum free-fatty acids, plasma catecholamines and the incidence of arrhythmias following acute myocardial infarction. *British Medical Journal*, **3**, 735–737.

Selye, H. (1946). The general adaptation syndrome and the diseases of adaptation. *Journal of Clinical Endocrinology*, **6**, 117–230.

Siggers, D. C., Slater, C., and Fluck, D. (1971). Serial plasma adrenaline and noradrenaline levels in myocardial infarction using a new double isotope technique. *British Heart Journal*, **33**, 878–883.

Taggart, P., Carruthers, M., and Somerville, W. (1973). ECG, plasma catecholamines and lipids, and their modification by Oxprenolol when speaking before an audience. *Lancet*, **2**, 341–346.

Taggart, P., Hedworth-Whitty, R., Carruthers, M., and Gordon, P. D. (1976). Observations on electrocardiogram and plasma catecholamines during dental procedures: the forgotten vagus. *British Medical Journal*, **2**, 787–789.

Taggart, P., Parkinson, P., and Carruthers, M. (1972). Cardiac responses to thermal, physical and emotional stress. *British Medical Journal*, **3**, 71–76.

Turton, M. B., and Deegan, T. (1973). Central and peripheral levels of plasma catecholamines, cortisol, insulin and non-esterified fatty acids. *Clinica Chimica Acta*, **48**, 347–352.

Turton, M. B., and Deegan, T. (1974). Circadian variations of plasma catecholamine, cortisol and immuno-reactive insulin concentrations in supine subjects. *Clinica Chimica Acta*, **55**, 389–397.

von Euler, U. S. (1964). Quantitation of stress by catecholamine analysis. *Clinical Pharmacology and Therapeutics*, **5**, 398–404.

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Changes in left ventricular free wall thickness in patients with ischaemic heart disease

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Continuous estimates of left ventricular free wall thickness were made from angiograms in 10 normal subjects and 20 patients with ischaemic heart disease. The time relations and extent of changes in wall thickness were compared with those in cavity area and transverse dimension, during isovolumic relaxation. In normal subjects, there was a mean reduction in wall thickness at this time of 0·3±0·1 cm (mean ±1 standard deviation), but maximum rate of wall thinning occurred after mitral valve opening, during the phase of rapid ventricular filling. In 10 patients with ischaemic heart disease and regions of abnormal outward movement of endocardium during isovolumic relaxation, there was a reduction in wall thickness of 0·8±0·1 cm before mitral valve opening ($P<0·001$ with respect to normal), with little change during the remainder of diastole. In 4 patients with regions of inward movement of endocardium during isovolumic relaxation, there was an abnormal increase in wall thickness of 0·5±0·2 cm at this time ($P<0·001$ with respect to normal), though the wall behaved normally after mitral valve opening. In 6 patients, endocardial movement and wall thickness changes were normal. It is concluded that changes in left ventricular cavity shape occurring during isovolumic relaxation in patients with coronary artery disease result from abnormal wall thickness changes related to the presence of regional ischaemia.

Changes in left ventricular wall thickness during the cardiac cycle can be measured by angiography or echocardiography, and several studies have described findings in normal subjects, and abnormalities in patients with left ventricular hypertrophy or ischaemic heart disease (Rackley *et al.*, 1964; Eber *et al.*, 1969; Hugenholtz *et al.*, 1969; Dodge *et al.*, 1974; Dumesnil *et al.*, 1974; Gould, *et al.*, 1976). There is, however, little information on the relation between changes in wall thickness and those of the left ventricular cavity, either concerning their extent or their timing. Since the thickness of the myocardium is considerable, particularly at end-systole when it may approximate to that of the transverse diameter of the left ventricle in normal subjects, it is clear that abnormalities of wall dynamics might have significant effects on cavity size and shape. The present study was, therefore, designed to measure, from angiograms, the relative effects of wall thickness changes and movement of the epicardium in determining the position of the endocardium of the anterior wall of the left ventricle throughout the cardiac cycle. Using an extension of methods devised to study regional abnormalities of wall movement (Gibson *et al.*, 1976), it was possible to investigate the interrelation between wall thickness and cavity size and shape in normal subjects and patients with ischaemic heart disease.

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Subjects and methods

DEFINITION OF TERMS

The left ventricular wall was defined as the structure lying between the epicardial and endocardial boundaries shown by the left ventriculogram. Wall thickness was defined as the distance between these boundaries, in a direction perpendicular to the endocardium at the site at which measurements were made, and the rate of change of wall thickness as the first derivative of this distance with respect to time. Regional changes in wall thickness measured in this way are referred to as wall dynamics (Dumesnil *et al.*, 1974). These definitions are consistent with the procedure employed, which is one of image analysis rather than a direct study of anatomical structures.

SUBJECTS

Thirty patients were studied by left ventriculography and coronary arteriography for pain thought to result from ischaemic heart disease. Twenty of them proved to have obstructive coronary artery disease, and in the remainder, haemodynamics, left ventriculogram, and coronary arteriograms were all normal. The latter group, termed 'normal', served as the basis for comparison with patients with ischaemic heart disease.

Left ventriculograms were obtained either in the posteroanterior or 30° right anterior oblique projection, using techniques that have previously been described (Gibson *et al.*, 1976). Coronary arteriography was then performed using Judkins' technique, when multiple views of the right and left coronary arteries were obtained. Only left ventriculograms showing clear delineation of endocardium and epicardium along the free heart border were studied.

ANALYSIS OF ANGIOGRAMS

Left ventriculograms were analysed using an extension of computer methods previously described (Gibson *et al.*, 1976), which aimed at delineating changes in left ventricular cavity and wall thickness, frame by frame. For each cine frame, the outline of the cavity was digitised, followed by a second line, representing the epicardial surface of the free wall over the region visible on the angiogram. This information, along with a fixed external reference point on the margin of the cine frame and calibration data from a grid exposed immediately after the angiogram at mid-chest level, was stored on disc for further calculations. Cavity area was calculated by numerical integration. In the group of patients with ischaemic heart disease, endocardial movement along the anterior wall was analysed using methods previously described. Of the 20 patients with ischaemic heart disease, there were: (1) 6 patients in whom anterior wall movement was normal with respect to both amplitude and timing; (2) 2 patients with only hypokinesis of the anterior wall; (3) 10 patients who had regions of abnormal outward movement before mitral valve opening: in all these patients, comparison could be made with a normally moving region of anterior wall on the same ventriculogram; and (4) 4 patients who had regions of abnormal inward movement before mitral valve opening: of these 1 also showed anterior hypokinesis and 2 abnormal outward movement elsewhere along the anterior wall.

Wall thickness changes were studied in two ways:

(1) The digitised outlines of cavity and epicardium for the beat to be studied were displayed on a Tektronix 4010 computer controlled display. A straight line was selected across the cavity so as to pass through the free wall and the cavity itself, approximately perpendicular to the walls. Plots were then made of changes with time of dimension and wall thickness and their corresponding rates of change. The time of mitral valve opening, determined as the frame in which unopacified dye from the left atrium first appeared within the left ventricular cavity, was superimposed on all traces, along with that of minimum cavity area. A representative example is shown in Fig. 1. From these plots, the following measurements were made: (a) end-diastolic and end-systolic wall thickness and cavity dimension, together with their peak rates of change during systole and diastole, (b) the extent of wall thinning between the time of maximum thickness and mitral valve opening (Table, 1), and

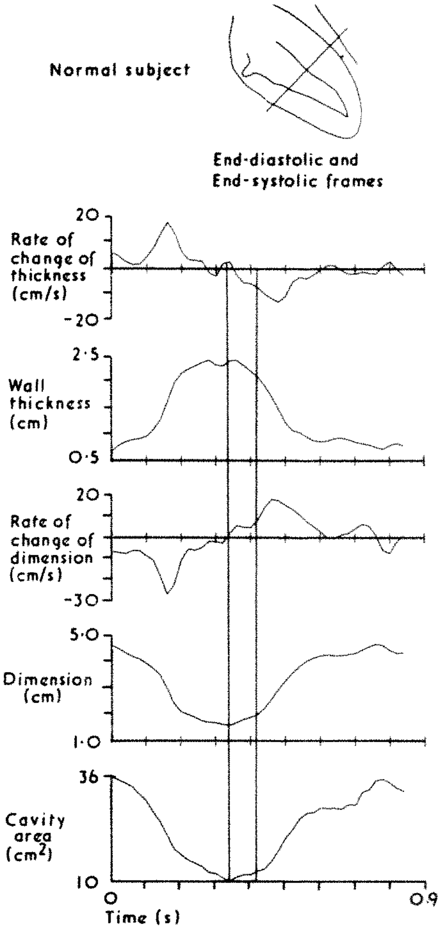

Fig. 1 *Measurements of cavity area, transverse dimension, and wall thickness in a normal subject. The vertical lines mark the times of minimum cavity area and mitral valve opening. The position of the transverse dimension and of the free wall epicardium digitised are indicated in relation to end-diastolic and end-systolic cavity outlines.*

Table

Group of patients (no. of subjects)		*Dimension* *End-diastolic* *cm*	*Systolic reduction* *cm*	*Peak systolic dD/dt* *cm/s*	*Peak diastolic dD/dt* *cm/s*
Normal subjects (10)		4·9 ±0·4	2·2 ±0·4	13 ±5	16 ±4
Ischaemic heart disease					
Normal isovolumic wall movement (6)		5·1 ±0·6	2·1 ±0·5	14 ±6	14 ±3
With abnormal outward wall movement in isovolumic relaxation (10)	Abnormal region of wall	5·0 ±0·8	1·9 ±0·5	12 ±2	13 ±4
	Normal region of wall	4·9 ±0·7	1·8 ±0·7	10 ±3	11 ±5
With abnormal inward wall movement in isovolumic relaxation (4)	Abnormal region of wall	4·4 ±0·5	2·1 ±0·2	12 ±4	15 ±3

1, wall thinning before mitral valve opening (mm); 2, maximum wall thickness to minimum cavity area (ms); 3, mitral valve opening to peak thinning rate (ms); 4, rapid thinning period (ms); 5, maximum wall thickness to peak thinning rate (ms).
*Significantly different from normal subjects ($P < 0{\cdot}01$ or 0·001).

the duration of the rapid thinning period, defined as the time interval between maximum wall thickness and the discontinuity marking the end of rapid thinning visible on all traces (Table, 4). The time interval from maximum wall thickness to the time of peak wall thinning rate was also recorded (Table, 5); (c) the relation between changes in wall thickness and events referable to the cavity as a whole was studied in terms of the interval between maximum wall thickness and minimum cavity area (Table, 2), and between mitral valve opening and the time of peak wall thinning rate (Table, 3); and (d) the change in transverse dimension between end-systole and end-diastole was compared with the corresponding change in wall thickness.

(2) The second method of display was aimed at providing a more comprehensive picture of local abnormalities of wall dynamics. This was based on a method devised for studying local movement around the endocardium of the left ventricular cavity. Forty equally spaced points were defined around the end-diastolic endocardial outline, starting from the border of the aorta adjacent to the mitral valve and proceeding anticlockwise, and from each the nearest point on the end-systolic outline was sought. Along each of the lines thus defined, endocardial position was measured for each cine frame, relative to the end-diastolic position, resulting in 40 plots of endocardial position against time throughout the cardiac cycle. In the region of free wall for which the epicardium was also digitised, these same lines were continued outwards, and the distance along them between endocardial and epicardial outlines measured, and also plotted against time throughout the cardiac cycle. Information about endocardial position was displayed as an isometric plot and identical methods were used to display changes in wall thickness, examples being given in Fig. 2 and 4.

Results

The results are given in detail in the Table.

NORMAL SUBJECTS

In the normal patients, end-diastolic dimension, measured at the level of the mitral valve, was 4·9±0·4 cm, with a reduction of 2·2±0·4 cm during systole. Peak systolic rate of shortening was 13±5 cm/s, and increase during diastole was 16±4 cm/s. End-diastolic wall thickness was 0·9±0·2 cm at this level of the ventricle, increasing to 2·0±0·5 at end-systole. The peak rate of increase in wall thickness was 9±4 cm/s, and maximum wall thickness was synchronous (±15 ms) with minimum cavity area (Table, 2 and Fig. 1). The peak rate of wall thinning was 10±4 cm/s and a distinct rapid thinning period could be identified, starting at the time of maximum wall thickness and ending with a discontinuity on the trace of the first derivative of wall thickness with time (Table, 4). This lasted 220±40 ms, with maximum rate of wall thinning occurring 110±40 ms after maximum wall thickness (Table, 5). During the interval between minimum cavity area and mitral valve opening, wall thickness fell by 0·3±0·1 cm (Table, 1). Mitral valve opening preceded peak thinning rate in 8 out of 10 patients, by 30±30 ms for the group as a whole (Table, 3). In these patients, changes in wall thickness were uniform throughout the cardiac cycle over the region of wall that could be studied. A representative isometric plot is shown in Fig. 2. There is uniform thickening during systole, slight thinning with isovolumic

Wall thickness					*Times (ms)*			
End-diastolic	*End-systolic*	*Peak systolic dW/dt*	*Peak diastolic dW/dt*	*1*	*2*	*3*	*4*	*5*
cm	*cm*	*cm/s*	*cm/s*	*mm*				
0·9	2·0	9	10	3	0	30	220	110
±0·2	±0·5	±4	±4	±1	±15	±30	±40	±40
0·8	1·8	10	8	4	0	20	210	110
±0·3	±0·3	±5	±2	±2	±10	±40	±40	±30
0·8	1·8	7	11	8*	±10	−80*	120*	60*
±0·2	±0·2	±2	±2	±1	±20	±40	±20	±20
0·9	2·1	8	9	3	0	40	200	110
±0·2	±0·3	±1	±3	±1	±30	±40	±60	±40
0·8	2·0	7	9	−5*	−80*	10	190	80
±0·2	±0·4	±2	±1	±2	±20	±20	±70	±20

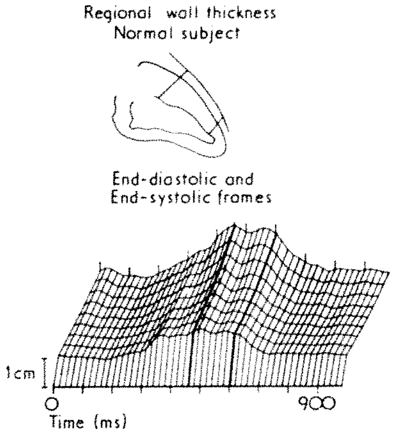

Fig. 2 *Multiple plots of wall thickness against time from a normal subject, showing pattern of wall dynamics along the region of free wall from the apex (front) towards the aortic root (back), as in the upper panel which shows end-systolic and end-diastolic outlines. Diagonal lines represent timing of successive cine frames, and accentuated lines minimum cavity area and mitral valve opening. Maximum wall thickness in individual plots is indicated by small vertical lines.*

relaxation, and a greatly increased rate of thinning after mitral valve opening. These appearances were seen in all normal subjects.

ISCHAEMIC HEART DISEASE

In 6 patients, left ventricular wall movement was normal, and in these patients, changes in wall thickness were also within normal limits, the results being shown in Table, 1.

Two patients showed hypokinesis of the anterior wall. End-diastolic wall thickness was normal in both, but the increases with systole were reduced to 0·3 cm and 0·5 cm, as were peak values of thickening to 2 and 4 cm/s, respectively. Neither patient showed a period of rapid thinning or significant change in wall thickness during the period of isovolumic relaxation.

Ten patients had normal systolic amplitude of wall movement, but excessive outward movement during isovolumic relaxation, in part of the free wall (Fig. 3). In these patients, it was possible to compare wall thickness dynamics of a normal region with those from a region where they were abnormal. In regions defined as normal, with respect to movement of endocardium, wall thickness changes were not significantly different in any way from

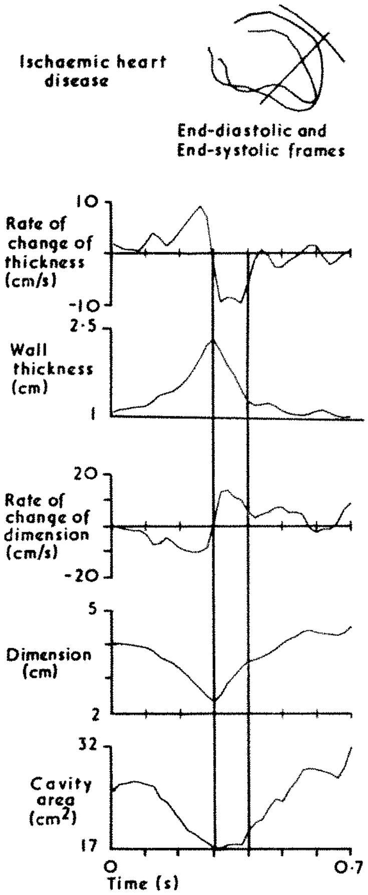

Fig. 3 *Measurements of cavity area, transverse dimension, and wall thickness from a patient with ischaemic heart disease. Layout as in Fig. 1. During isovolumic relaxation, there is significant increase in dimension along with a reduction in wall thickness.*

those occurring in normal subjects (Table). For regions showing abnormal isovolumic movement, however, significant differences were present, both from normal subjects, and from normal regions of the same ventricle (Fig. 4). There was a considerable reduction of $0{\cdot}8 \pm 0{\cdot}1$ cm in wall thickness before mitral valve opening ($P < 0{\cdot}001$), while peak thinning rate was always recorded before mitral valve opening ($P < 0{\cdot}01$), though its value was normal. As in the normal group, peak wall thickness coincided with minimum cavity area, but peak thinning rate occurred within 60 ± 20 ms, significantly earlier than normal ($P < 0{\cdot}01$), and the rapid thinning period lasted only 120 ± 20 ms ($P < 0{\cdot}001$). In these regions, the timing of the end of rapid thinning was particularly clear, since in 8 out of 10 patients, a short period of increasing wall thickness occurred at this time, approximately synchronous with mitral valve opening. This reversal was not apparent in normal regions of the same ventricle.

In 5 patients, abnormal inward movement occurred during isovolumic relaxation (Fig. 5). This was associated with $0{\cdot}5 \pm 0{\cdot}2$ cm increase in wall thickness after the time of minimum cavity area, the reverse of the normal pattern. Maximum wall thickness thus followed minimum cavity area by 80 ± 20 ms, instead of being synchronous with it ($P < 0{\cdot}01$). The duration of the rapid thinning period, and the time from maximum wall thickness to maximum thinning rate, however, were normal. In all these cases, normal peak thickening rates were recorded, but they were abnormal in timing, being after minimum cavity area, and thus falling in the period of isovolumic relaxation.

The relation between changes in wall thickness and dimension were investigated in the group as a whole. There was significant correlation between the reduction in transverse left ventricular dimension and the increase in wall thickness between end-diastole and end-systole, given by the equation:

$$\text{(Reduction in dimension)} = 1{\cdot}07\ \text{(increase in wall thickness)} + 0{\cdot}9\ \text{cm}$$

$$r = 0{\cdot}72,\ \text{standard error of the estimate } 0{\cdot}25\ \text{cm.}$$

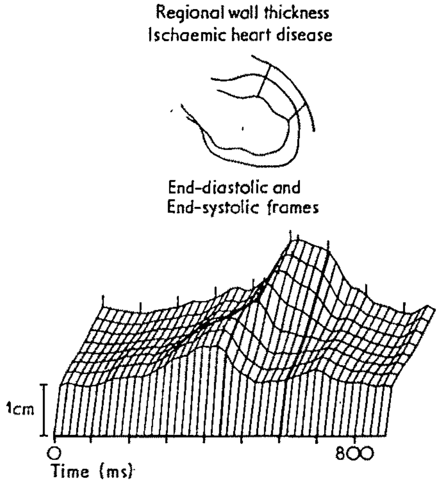

Fig. 4 *Multiple plots of wall thickness against time from a patient with ischaemic heart disease. Layout as in Fig. 2. Towards the apex, there is abnormal wall thinning before mitral valve opening, but the pattern becomes normal higher up the wall.*

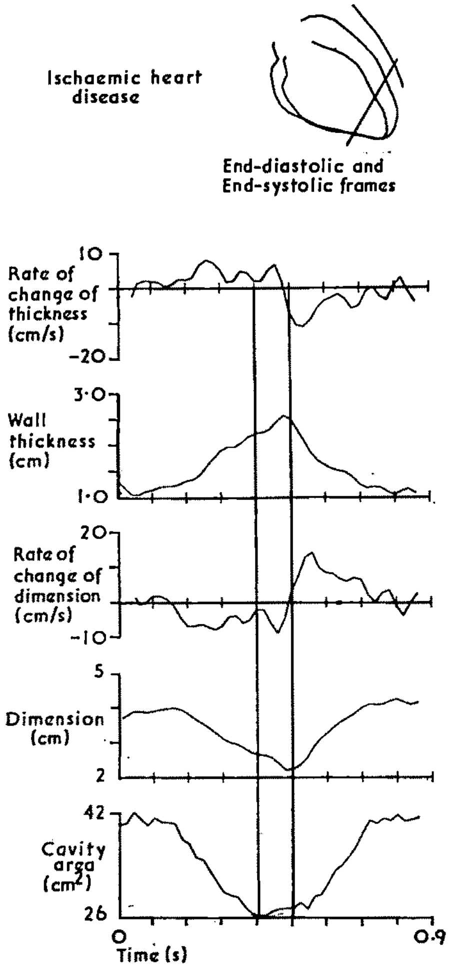

Fig. 5 *Plots of cavity area, transverse dimension, and wall thickness from a patient with ischaemic heart disease. Layout as in Fig. 1. There is a reduction in dimension during isovolumic relaxation, along with an increase in wall thickness.*

Peak rates of change of dimension during systole and diastole were also correlated with the corresponding rates of change of wall thickness, the appropriate regression equations being:

$$(\text{Peak systolic } dD/dt) = 1{\cdot}2\ (\text{peak systolic } dW/dt) + 2{\cdot}1 \text{ cm/s}$$

$r = 0{\cdot}82$, standard error of the estimate $= 3{\cdot}2$ cm/s

$$(\text{Peak diastolic } dD/dt) = 0{\cdot}76\ (\text{peak diastolic } dW/dt) + 7{\cdot}1 \text{ cm/s}$$

$r = 0{\cdot}50$, standard error of the estimate $= 2{\cdot}8$ cm/s, where D = instantaneous cavity dimension, and W = wall thickness.

Discussion

Measurements of left ventricular wall thickness derived from angiograms differ from those obtained using ultrasound or radiographic observations of metal markers in experimental animals. Though all methods give similar estimates of wall thickness at end-diastole, at end-systole angiographic values are appreciably greater, probably because of endothelial infolding of the wall, so that sonar transducers or markers sutured to the endocardium may become separated from the cavity (Mitchell *et al.*, 1969; Guntheroth, 1974; Rankin *et al.*, 1976). We have made no attempt to circumvent this discrepancy. Angiography outlines the region accessible to blood throughout the cardiac cycle, and shows that this endothelial infolding is an important mechanism by which cavity size is reduced in systole. Methods based on the constancy of left ventricular mass, assumed uniformity of wall thickness, and ellipsoidal geometry at end-systole have not been used (Rackley *et al.*, 1964; Hugenholtz *et al.*, 1969). They would have been unsuitable for assessing abnormalities of timing, since, by definition, derived wall thickness changes must be synchronous with the corresponding changes in cavity volume. Such models are particularly unsuitable in patients with ischaemic heart disease, where the pattern of left ventricular involvement is non-uniform. Finally, on more general grounds, errors in measurement of wall thickness at end-systole result from uncertainty about endocardial rather than epicardial position, which implies corresponding uncertainty about the cavity boundary. Values of cavity size so obtained would thus be critically affected by the very uncertainty that they are being used to correct.

The present method of measuring left ventricular wall thickness has confirmed previous estimates of thickness at end-diastole and end-systole, and of peak rate of increase during systole, using comparable techniques (Eber *et al.*, 1969; Dumesnil *et al.*, 1974). The peak rate of change during diastole was similar to that occurring during systole, and a well-defined period of rapid thinning could be identified. In normal subjects, the timing of events in the wall was closely related to changes in cavity area (Fig. 1). Maximum wall thickness was synchronous with minimum cavity area. During isovolumic relaxation, there was a small reduction in wall thickness, but after mitral valve opening, the rate at which the wall became thinner increased, synchronous with rapid ventricular filling. The extent and timing of these changes were uniform over the region of free wall accessible to study by angiography (Fig. 2). These observations are similar to those of Rankin *et al.* (1976) in dogs, both in showing maximum wall thickness at end-ejection, and also a significant reduction in wall thickness during isovolumic relaxation, though Rankin found the extent of systolic wall thickening to be less, and that the minor axis tends to shorten rather than increase immediately before mitral valve opening.

A number of disturbances of left ventricular wall dynamics were present in patients with ischaemic heart disease. As has previously been found (Eber *et al.*, 1969; Dumesnil *et al.*, 1974), localised reduction in the amplitude of inward movement of endocardium during systole was associated with a corresponding reduction in the extent of free wall thickening, and of peak rate of increase of wall thickness during systole. More common, in the present series of patients, were disturbances of the close time relations between events in the wall and those referable to the cavity as a whole. Regions showing these disturbed time relations often behaved normally during systole, but abnormally during isovolumic relaxation, defined as the interval between minimum cavity area and mitral valve opening. These abnormal time relations of wall thickness changes closely resembled abnormalities of endocardial movement previously described (Altieri *et al.*, 1973; Ruttley *et al.*, 1974; Gibson *et al.*, 1976). The latter are of two types: inward movement during isovolumic relaxation, apparently reflecting the effects of local ischaemia, and outward movement in regions with normal systolic function, representing a compensatory phenomenon. It is clear from the present study that these abnormalities, previously defined only in terms of endocardial movement, have, as their basis, localised abnormalities of wall behaviour. An abnormal increase in wall thickness after the time of minimum cavity area caused inward movement during isovolumic relaxation. Conversely, outward endocardial movement before mitral valve opening resulted from a premature reduction in wall thickness, with peak wall thinning rate being recorded before the start of ventricular filling. These abnormalities were confined to regions of the ventricle showing abnormal endocardial behaviour, and were not found elsewhere in the cavity where its pattern of movement was normal. Their extent was so great, particularly in regions showing outward endocardial movement during isovolumic relaxation, that they could not have been explained solely on the basis of reversal of endothelial infolding, but represented virtual completion of the diastolic reduction in wall thickness before mitral valve opening. These results thus allow previous observations to be extended (Gibson *et al.*, 1976), and indicate that when localised ischaemia causes inward movement of endocardium during isovolumic relaxation, it does so by causing a transient increase in wall thickness rather than by any movement of epicardium. This process is associated with compensatory thinning of the wall and outward movement of endocardium in normal regions. It is these abnormalities within the wall itself that cause changes in left ventricular cavity shape previously described only in terms of their effect on endocardial position.

In normal subjects, there appeared to be a close reciprocal relation in diastole between changes in cavity size and wall thickness, with rapid ventricular filling corresponding to the period of rapid thinning. In patients showing abnormal outward movement of endocardium before mitral valve opening, however, the period of rapid wall thinning could be dissociated from that of rapid filling, since it occurred before mitral valve opening. This dissociation between events in wall and cavity suggests that rapid thinning may be as much a property of the myocardium itself as the direct result of an increase in cavity volume. Wall thinning did occur significantly more slowly, however, when it followed mitral valve opening, suggesting that in normal circumstances filling rate might exert a limiting effect on it, which was not present when it was the direct result of delayed relaxation elsewhere. Studies of changes in wall thickness in the presence of other abnormalities of ventricular filling might shed further light on this problem.

It is apparent, therefore, that measurements of wall thickness may facilitate the study of regional left ventricular function. They can be used to define localised abnormalities of cavity outline independently of any arbitrary reference point used for aligning successive cine frames, and have confirmed previous observations based on endocardial position alone. Indeed, the similarity between the two methods suggests that the theoretical possibility of significant transverse and rotational movement of the heart within the thorax is not an important one in the patients studied. In addition, abnormal wall thickness changes may themselves reflect local ischaemia, and give rise to disturbances of appreciable functional significance during isovolumic relaxation in patients with coronary artery disease. The technical resources required for these studies are modest, and their further extension seems indicated.

The computing equipment used in this study was provided by the D.H.S.S. as part of their experimental programme.

References

Altieri, P. I., Wilt, S. M., and Leighton, R. F. (1973). Left ventricular wall motion during the isovolumic relaxation period. *Circulation*, **48**, 499–505.

Dodge, H. T., Frimer, M., and Stewart, D. K. (1974). Functional evaluation of the hypertrophied heart in man. *Circulation Research*, **34–35**, Suppl. II, 122–127.

Dumesnil, J. G., Ritman, E. L., Frye, R. L., Gau, G. T., Rutherford, B. D., and Davis, G. D. (1974). Quantitative determination of regional left ventricular wall dynamics by Roentgen videometry. *Circulation*, **50**, 700–708.

Eber, L. M., Greenberg, H. M., Cooke, J. M., and Gorlin, R. (1969). Dynamic changes in left ventricular free wall thickness in the human heart. *Circulation*, **39**, 455–464.

Gibson, D. G., Prewitt, T. A., and Brown, D. J. (1976). Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *British Heart Journal*, **38**, 1010–1019.

Gould, K. L., Kennedy, J. W., Frimer, M., Pollack, G. H., and Dodge, H. T. (1976). Analysis of wall dynamics and directional components of left ventricular contraction in man. *American Journal of Cardiology*, **38**, 322–331.

Guntheroth, W. G. (1974). Changes in left ventricular wall thickness during the cardiac cycle. *Journal of Applied Physiology*, **36**, 208–312.

Hugenholtz, P. G., Kaplan, K., and Hull, E. (1969). Determination of left ventricular wall thickness by angiocardiography. *American Heart Journal*, **78**, 513–522.

Mitchell, J. H., Wildenthal, K., and Mullins, C. B. (1969). Geometrical studies of the left ventricle utilizing biplane cinefluorography. *Federation Proceedings*, **28**, 1334–1343.

Rackley, C. E., Dodge, H. T., Coble, Y. D., and Hay, R. E. (1964). Method for determining left ventricular mass in man. *Circulation*, **29**, 666–671.

Rankin, J. S., McHale, P. A., Arentzen, C. E., Greenfield, J., Jr., and Anderson, R. W. (1976). Three dimensional dynamic geometry of the left ventricle in the conscious dog. *Circulation Research*, **39**, 304–313.

Ruttley, M. S., Adams, D. F., Cohn, P. F., and Abrams, H. L. (1974). Shape and volume changes during 'isovolumetric relaxation' in normal and asynergic ventricles. *Circulation*, **50**, 306–316.

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Prompt return to normal of depressed right ventricular ejection fraction in acute inferior infarction[1,2]

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A relatively simple, bedside, radionuclide technique has been developed to measure right ventricular ejection fraction. This technique uses a collimated scintillation probe (5×5 cm sodium iodide crystal) and $^{113\mathrm{m}}$*Indium injected into the superior vena cava to record a right ventricular time-activity curve. The radionuclide method was validated in 34 men (14 normals, 20 with coronary artery disease) with biplane right ventriculography ($r=0{\cdot}82$). Using this radionuclide method right ventricular ejection fraction was measured in 26 men (average age 51 years) with an acute transmural myocardial infarction. Right ventricular ejection fraction was initially depressed (0·40±0·02; mean±SEM; normal 0·57±0·01) in all of 11 men with an acute inferior infarction but returned to normal by the third day in 10 of them (0·58±0·01; NS). In the 15 men with an acute anterior infarction the average right ventricular ejection fraction was normal initially (0·54±0·01; NS) and individually 10 of 15 had a normal ejection fraction. Left ventricular ejection fraction was initially depressed in all patients and only 4 of 34 (12%) had returned to normal at the third day. These results suggest that right ventricular ejection fraction is regularly depressed in patients with an acute inferior infarction but normal in those with an anterior infarction. Right ventricular performance rapidly improves after inferior infarction; whereas less improvement occurs in left ventricular ejection fraction.*

Left ventricular ejection fraction has been found to be regularly depressed in acute myocardial infarction both early (Kostuk *et al.*, 1973) and late after infarction (Rackley *et al.*, 1970; Hamilton *et al.*, 1972; Stewart *et al.*, 1974). Kostuk and associates (1973) have shown that a relation exists between left ventricular ejection fraction and myocardial infarct size, as measured with serial determinations of serum creatine kinase activity. Though a disparity between right and left ventricular filling pressures in acute myocardial infarction has been appreciated (Forrester *et al.*, 1971) and infarction of the right ventricle has been recognised both clinically (Cohn *et al.*, 1974; Rotman *et al.*, 1974) and pathologically (Wartman and Hellerstein, 1948; Wade, 1959; Erhardt, 1974), relatively little attention has been paid to right ventricular performance in either chronic coronary artery disease or acute myocardial infarction.

We had previously developed a radionuclide method for estimating left ventricular ejection fraction which uses a portable scintillation probe (Steele *et al.*, 1974). The purpose of the present study was to develop a radionuclide method for estimating right ventricular ejection fraction and to apply this technique to the serial study of patients with acute myocardial infarction.

Subjects and methods

Right ventricular ejection fraction was measured from radiocardiograms obtained using a collimated scintillation probe by a modification of a radionuclide method for estimating left ventricular ejection fraction (Steele *et al.*, 1974). To measure right ventricular ejection fraction about 1 millicurie of $^{113\mathrm{m}}$Indium was injected into a catheter placed in the superior vena cava and flushed with saline. Using a scintillation probe (5×5 cm sodium iodide crystal) placed over the midpoint of

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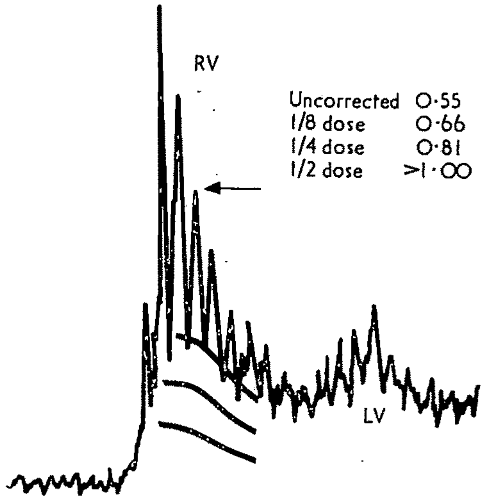

Fig. *Time-activity curve recorded after injection of ^{113m}Indium into the superior vena cava. The right ventricular (RV) and left ventricular (LV) portions of the curve are indicated. Using a shield (eclipse) collimation (see text) a series of curves was obtained for background correction; these are drawn under the right ventricular portion of the initial curve. Using the background curve (uppermost) obtained with half the initial dose of ^{113m}Indium yields an ejection fraction of >1·00 (average of 3 beats after end-diastolic point indicated by the arrow). The ejection fraction calculated using the curve (middle one) obtained with quarter the initial dose is also too high, while use of the curve (lowermost) obtained with eighth of the initial dose yields correct the ejection fraction (0·66) as judged from that computed using contrast cineventriculography.*

the right ventricle in the anteroposterior projection, with the patient supine, a time-activity curve was recorded (Fig.). This curve was obtained with a ring collimator (3·5 cm port) as previously described (Steele *et al.*, 1974). After recording the right ventricular time-activity curve, $\frac{1}{8}$ of the initial dose of ^{113m}Indium was injected into the catheter and flushed and a second curve was obtained using a 5·5 cm circular shield collimator (Fig.). This second curve represents the count rate obtained from radionuclide-containing tissues which surround the right ventricle as the shield collimation rejects counts from the underlying right ventricle. Van Dyke and associates (1972) have indicated the need to correct a cardiac chamber time-activity curve for the effect of scattered radiation in order to measure the ejection fraction accurately (Van Dyke *et al.*, 1972).

To measure left ventricular ejection fraction, the same collimation was used but the probe was positioned over the midpoint of the left ventricle in the anteroposterior projection with the patient supine. About 1 mCi ^{113m}Indium was injected through the superior vena caval catheter and flushed with saline. A left ventricular time-activity curve was obtained and then a second curve was recorded with the shield collimation using half the initial dose of radionuclide. In these studies left ventricular ejection fractions were measured immediately after the right.

Accurate positioning of the probe was necessary to obtain a satisfactory record. The midpoints of the right and left ventricle were estimated from a supine anteroposterior chest film obtained just before the radionuclide study. Confirmation of correct probe position was obtained from the time-activity curve as each measurement of ejection fraction (beat to beat variation) should not differ by more than 10 per cent.

Ejection fraction was calculated as the fractional fall in count-rate from end-diastole to end-systole divided by the end-diastolic count rate. The correct baseline (corrected for scattered radiation) for measuring the end-diastolic count rate was obtained by matching the troughs of the 2 time-activity curves, port and shield, and drawing the shield record on the port recording (Fig.). Ejection fraction was calculated for as many beats as possible and averaged. This always included at least 2 beats for the right ventricle and 3 for the left ventricle.

In 34 men who underwent cardiac catheterisation and coronary arteriography for evaluation of chest pain, right ventricular ejection fraction was measured with the radionuclide method and from biplane (anteroposterior and steep left anterior oblique) contrast cineventriculograms using the area measurement method of Arcilla and associates (1971). Twenty men were found to have coronary artery disease and 14 had normal coronary arteriograms.

To derive the right ventricular ejection fraction from the ventriculograms, the outline of the right ventricle was traced from the projected end-diastolic (largest) and end-systolic (smallest) frames in both the anteroposterior (AP) and left anterior oblique (LAO) projections. The right ventricular volume (V) was calculated, using the planimetered areas of the anteroposterior and left anterior oblique projections with the maximum apex base dimension (L) in the LAO projection, as:

$$V=\pi L M_{LAO} \cdot M_{AP}/6 \qquad (1)$$

where M, the minor axis, was calculated from the planimetered areas (A) using the ellipse formula as:

$$M_{LAO}=4A_{LAO}/\pi L \qquad (2)$$

and

$$M_{AP}=4\,A_{AP}/\pi L \qquad (3)$$

Using this method, Arcilla *et al.* (1971) noted good correlation between contrast ventriculography and right ventricular casts.

In another group of 21 men without cardiac disease and with normal coronary arteriograms, left ventricular ejection fraction was measured with the scintillation probe and from single plane (right anterior oblique) contrast left cineventriculograms. The contrast ventriculograms were analysed using area length concepts (Dodge *et al.*, 1960; Kennedy *et al.*, 1970). The left ventricular silhouette was traced at end-diastole and end-systole and ejection fraction was computed as the difference between the end-diastolic and end-systolic volume divided by the end-diastolic volume, with volume (V) calculated as:

$$V = \pi L M^2/6 \qquad (4)$$

where M was the minor axis in the right anterior oblique projection.

Serial radiograms were obtained from 26 men with an acute transmural infarction. These men ranged in age from 39 to 66 years (average 51 years) and had clinical and electrocardiographic evidence (Q waves in at least 3 leads) of acute anterior or inferior infarction of less than 24 hours duration. No patient had clinical or electrocardiographic evidence of previous myocardial infarction. All patients were studied at their bedside in the cardiac care unit as soon as possible after admission and initial stabilisation.

Radiocardiograms were recorded on the first, second, third, and twelfth day after infarction. All patients were in normal sinus rhythm and none had clinical evidence of mitral regurgitation. All patients were in Killip class I, II, or III (Killip, 1968) and none was in shock. Diuretics, digitalis, nitrates, or catecholamines were not administered at any time during their stay in hospital. All patients gave their informed consent for performance of these studies.

Eleven men had acute inferior infarction and 15 had acute anterior infarction. None had previous infarction and there were no differences between the two groups in age, Killip class, history of chronic obstructive airways disease, or systemic hypertension (Table). All patients survived to the twelfth day, with 2 subsequent deaths in men with anterior infarction.

Table *Clinical comparison of men with inferior and anterior infarction*

	Inferior infarction (N=11)	*Anterior infarction (N=15)*
Average patient age (y)	49	52
Killip Class III	2	3
Clinical evidence of chronic obstructive airways disease	2	1
History or clinical evidence of systemic arterial hypertension	3	2

Results

In the 14 normal men, right ventricular ejection fraction, estimated with the scintillation probe, averaged 0·57 ±0·01 (±SEM) with a range of 0·53 to 0·62. Using two standard deviations about the mean, the normal range was computed as 0·52 to 0·62. Right ventricular ejection fractions obtained in these 14 men from their ventriculograms had values with an average of 0·58 ±0·63. In the 34 men, right ventricular ejection fraction was measured with the scintillation probe correlated ($r=0{\cdot}82$) with the right ventricular ejection fraction measured from contrast cineventriculography.

Left ventricular ejection fraction radiocardiographically measured in 21 normal men averaged 0·66 with a range of 0·57 to 0·77. Using two standard deviations the range of normal left ventricular ejection fraction was 0·56 to 0·76. The cineangiocardiographic left ventricular ejection fraction in these 21 men averaged 0·66 and the range was 0·55 to 0·76. The left ventricular ejection fraction measured with the radionuclide method correlated with the left ventricular ejection fraction obtained from single plane cineangiography ($M=0{\cdot}91$; $N=48$).

Serial radiocardiographic determinations of right and left ventricular ejection fraction (1–3 repeat studies in a 1–2 hour period) were undertaken in 12 men. Variation of average was always less than 10 per cent. Thus, the radionculide method for estimating right and left ventricular ejection fractions seems to be accurate as measured against cineventriculography and to be reproducible.

The right ventricular ejection fraction was depressed ($<0{\cdot}52$) on the first day in all the men with acute inferior infarction and the average value ±SEM was 0·50 ±0·02; $P<0{\cdot}001$. By the second day the average right ventricular ejection fraction was normal (0·53 ±0·01) and 10 of the 11 patients had an increase in right ventricular ejection fraction of 0·05 or more. Some further increase was noted on the third day (0·58 ±0·01) but there was no further change from day 3 to 12 (0·58 ±0·01). At the third day only 1 patient had an abnormal right ventricular ejection fraction and this was only barely abnormal at 0·51. On the twelfth day all patients had a normal right ventricular ejection fraction.

In the men with acute anterior infarction the average right ventricular ejection fraction on the first day was normal (0·54 ±0·01) but in 5 of the 15 it was depressed. By the second day it averaged 0·56 ±0·01 and in 2 of the 5 where it was initially depressed it was now normal. On the third day 2 of the 15 had a depressed right ventricular ejection fraction and the average was 0·56±0·01 which persisted to the twelfth day (0·56±0·01). Thus, right ventricular ejection fraction was regularly depressed early after acute inferior infarction and promptly improved, while in acute anterior infarction the ejection fraction was less often decreased and failed to return to normal in some patients.

The average left ventricular ejection fraction for the 11 men with acute inferior infarction was depressed (0·44±0·02 days; $P<0·001$) and individually all had a decreased left ventricular ejection fraction. Some improvement was noted with time, averaging 0·50±0·01 on the second, 0·51±0·01 on the third, and 0·52±0·01 on the twelfth day after infarction. Only 2 men had a return to normal of the left ventricular ejection fraction (>0·55) on the twelfth day and only 1 of these on the third day.

After acute anterior infarction the left ventricular ejection fraction was depressed in all patients and averaged 0·39±0·02 ($P<0·001$) on day 1. Some increase in average ejection fraction was noted on day 2 (0·43±0·02), day 3 (0·45±0·02), and day 12 (0·46±0·02), but only 2 patients had a normal left ventricular ejection fraction on day 12 and these 2 were also normal on the third day. Thus, left ventricular ejection fraction did not appear to have the same potential for prompt increase as right ventricular ejection fraction after acute myocardial infarction. The 2 men who subsequently died had distinct depression of their left ventricular ejection fraction (0·28, 0·33) and had no improvement during the 12 days that they were studied.

Discussion

The radionuclide technique described in this report seems to measure right ventricular ejection fraction accurately. Time-activity curves of the right ventricle should accurately reflect changes in volume if the radionuclide is properly mixed within the chamber, as the volume estimated from the count rate does not depend on the geometry of the chamber. Injection of radionuclide into the superior vena cava should provide adequate mixing as another chamber, the right atrium, is traversed before entry of tracer into right ventricle. A number of contrast angiocardiographic methods have been developed for estimating right ventricular volume which use several geometric models for the right ventricle (Arcilla *et al.*, 1971; Graham *et al.*, 1973; Ferlinz *et al.*, 1975). All have been shown to be relatively accurate when compared with casts of the right ventricle. The advantages of the radionuclide technique presented in this report are its relative simplicity, portability, and applicability to serial study.

Right ventricular time-activity curves must be corrected for the effect of scattered radiation if they are to be used to estimate ejection fraction. Radiation scatter in tissues occurs and consequently the time-activity curve recorded from the right ventricle contains counts from tissues surrounding this chamber. Therefore, a second time-activity curve is recorded with the right ventricle shielded. This recording reflects counts from tissues which surround the right ventricle.

Using the scintillation probe method for measuring left ventricular ejection fraction, with injection of radionuclide into the superior vena cava such that it traverses the pulmonary circulation, one-half of the initial dose of ^{113m}Indium was used with the second injection (shield or eclipse tracing) to correct for scattered radiation. In the case of the right ventricle, one-eighth of the initial dose was found to provide the best estimate for calculation of ejection fraction (Fig.) The apparent lessened contribution of radiation scatter to the right ventricular time-activity curve as compared with the left ventricular curve probably reflects the absence of radionuclide within the pulmonary vasculature.

In our patients with acute inferior infarction all had an early decrease in right ventricular ejection fraction with a prompt improvement by the second day after infarction in 10 of 11 men. By the third day after infarction the right ventricular ejection fraction was normal in all but one patient. In another group of men with chronic coronary artery disease we found right ventricular ejection fraction to be normal in 22 of 29 (76%) patients with a history of inferior infraction, and 4 of the 7 with depressed right ventricular ejection fraction had triple vessel coronary artery disease on coronary arteriography (Steele *et al.*, 1976). In men with acute anterior infarction, right ventricular performance was generally preserved.

The blood supply of the right ventricle is usually derived from the right coronary artery. It is, therefore, not surprising that right ventricular performance is compromised in acute inferior infarction. It is of interest, however, how rapidly right ventricular ejection fraction improves. It is not certain which of several possible factors are responsible for this prompt improvement in performance. The right ventricular myocardium receives blood both during systole and diastole, whereas the left ventricular myocardium receives flow only during diastole (Wearn, 1941; Marshall and Shepherd, 1968). In addition the right ventricle can receive flow directly through the thebesian vessels and collateral coronary blood flow is more extensively developed for the right than the left ventricle (Zaus and Kearns, 1952).

Rigo and associates (1975) found increases of right ventricular end-diastolic volume early after infarction in patients with acute inferior infarction and a normal right ventricular end-diastolic volume in patients with an acute anterior infarction. Of 14 patients with inferior infarction, 6 had an increased end-diastolic volume. These investigators used an electrocardiographically gated radionuclide technique.

Of additional interest, though of no particular surprise, is the fact that left ventricular ejection was decreased in all of our patients with acute infarction. Some early improvement in left ventricular ejection fraction was noted, but not nearly as strikingly as for the right ventricle. Kostuk and associates have performed serial measurement of left ventricular ejection fraction in 55 patients with acute infarction and noted improvement in ejection fraction in 30 (Kostuk *et al.*, 1973).

As discussed by Cohn *et al.* (1974) and Rigo *et al.* (1975) appreciation of the fact that right ventricular dysfunction might contribute to hypotension and shock after acute infarction is an important consideration in the management of these patients. The opportunity to assess right ventricular function at the bedside of these patients using the relatively simple radionuclide technique of Rigo *et al.* (1975) or the scintillation probe method discussed in this report should usefully complement their haemodynamic assessment.

References

Arcilla, R. A., Tsai, P., Thilenius, O., and Ranniger, L. (1971). Angiographic method for volume estimation of right and left ventricles. *Chest*, **60**, 446–454.

Cohn, J. N., Guiha, N. H., Broder, M. I., and Limas, C. J. (1974). Right ventricular infarction. Clinical and hemodynamic features. *American Journal of Cardiology*, **33**, 209–214.

Dodge, H. T. Sandler, H., Ballew, D. W., and Lord, J. D., Jr. (1960). The use of biplane angiocardiography for the measurement of left ventricular volume in man. *American Heart Journal*, **60**, 762–776.

Erhardt, L. R. (1974). Clinical and pathological observations in different types of acute myocardial infarction. *Acta Medica Scandinavica*, Suppl. 560.

Ferlinz, J., Gorlin, R., Cohn, P. F., and Herman, M. V. (1975). Right ventricular performance in patients with coronary artery disease. *Circulation*, **52**, 608–615.

Forrester, J. S., Diamond, G., McHugh, T. J., and Swan, H. J. C. (1971). Filling pressures in the right and left sides of the heart in acute myocardial infarction. A reappraisal of central-venous-pressure monitoring. *New England Journal of Medicine*, **285**, 190–193.

Graham, T. P., Jr., Jarmakani, J. M., Atwood, G. F., and Canent, R. V., Jr. (1973). Right ventricular volume determinations in children. Normal values and observations with volume or pressure overload. *Circulation*, **47**, 144–153.

Hamilton, G. W., Murray, J. A., and Kennedy, J. W. (1972). Quantitative angiocardiography in ischemic heart disease: the spectrum of abnormal left ventricular function and the role of abnormally contracting segments. *Circulation*, **45**, 1065–1080.

Kennedy, J. W., Trenholme, S. E., and Kasser, I. S. (1970). Left ventricular volume and mass from single-plane cineangiocardiogram. A comparison of anteroposterior and right anterior oblique methods. *American Heart Journal*, **80**, 343–352.

Killip, T. (1968). Coronary care units, current policies and results. In *Acute Myocardial Infarction*, p. 23, Ed. by D. G. Julian and M. F. Oliver. Williams and Wilkins, Baltimore.

Kostuk, W. J., Ehsani, A. A., Karliner, J. S., Ashburn, W. L., Peterson, K. L., Ross, J., Jr., and Sobel, B. E. (1973). Left ventricular performance after myocardial infarction assessed by radioisotope angiocardiography. *Circulation*, **47**, 242–249.

Marshall, R. J., and Shepherd, J. T. (1968). *Cardiac Function in Health and Disease*, p. 186. W. B. Saunders, Philadelphia.

Rackley, C. E., Dear, H. D., Baxley, W. A., Jones, W. B., and Dodge, H. T. (1970). Left ventricular chamber volume, mass and function in severe coronary artery disease. *Circulation*, **41**, 605–613.

Rigo, P., Murray, M., Taylor, D. R., Weisfeldt, M. L., Kelly, D. T., Strauss, H. W., and Pitt, B. (1975). Right ventricular dysfunction detected by gated scintiphotography in patients with acute inferior myocardial infarction. *Circulation*, **52**, 268–274.

Rotman, M., Ratliff, N. B., and Hawley, J. (1974). Right ventricular infarction: a haemodynamic diagnosis. *British Heart Journal*, **36**, 941–944.

Steele, P., Kirch, D., LeFree, M., and Battock, D. (1976). Measurement of right and left ventricular ejection fractions by radionuclide angiocardiography in coronary artery disease. *Chest*, **70**, 51–56.

Steele, P. P., Van Dyke, D., Trow, R. S., Anger, H. O., and Davies, H. (1974). Simple and safe bedside method for serial measurement of left ventricular ejection fraction, cardiac output and pulmonary blood volume. *British Heart Journal*, **36**, 122–131.

Stewart, D. K., Hamilton, G. W., Murray, J. A., and Kennedy, J. W. (1974). Left ventricular function and coronary artery anatomy before and after myocardial infarction. A study of six cases. *Circulation*, **49**, 47–54.

Van Dyke, D., Anger, H. O., Sullivan, R. W., Vetter, W. R., Yano, Y., and Parker, H. G. (1972). Cardiac evaluation from radioisotope dynamics. *Journal of Nuclear Medicine*, **13**, 585–592.

Wade, W. G. (1959). The pathogenesis of infarction of the right ventricle. *British Heart Journal*, **21**, 545–554.

Wartman, W. B., and Hellerstein, H. K. (1948). The incidence of heart disease in 2,000 consecutive autopsies. *Annals of Internal Medicine*, **28**, 41–65.

Wearn, J. T. (1941). Morphological and functional alterations of the coronary circulation. *Bulletin of the New York Academy of Medicine*, **17**, 754–777.

Zaus, E. A., and Kearns, W. M. (1952). Massive infarction of the right ventricle and atrium. Report of a case. *Circulation*, **6**, 593–598.

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Relation between apex cardiographic and internal indices of left ventricular relaxation in man[1]

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In 19 patients the left apex cardiogram was recorded by a transducer with infinite time constant; at the same time left ventricular (tip manometer) and aortic pressures were recorded during cardiac catheterisation. The relation between two relaxation time intervals in the apex cardiogram and haemodynamic as well as angiocardiographic indices of left ventricular performance were studied. These apex cardiographic time intervals were: (1) the time from the onset of the aortic component of the second heart sound (S_2) in the phonocardiogram to the negative peak of the first derivative (dA/dt) of the apex cardiogram, termed early apex cardiographic relaxation time, and (2) the time from S_2 to the point where dA/dt after having reached its negative peak ascends to the zero line, termed total apex cardiographic relaxation time.

In 100 normal subjects early apex cardiographic relaxation time averaged 3±12 (±1 SD) ms and total apex cardiographic relaxation time was 93±16 ms. In 11 patients with non-obstructive cardiomyopathy and decreased left ventricular function early and total apex cardiographic relaxation times were significantly ($P<0{\cdot}001$) prolonged (52±23 ms and 152±23 ms, respectively), whereas in 8 patients without or with only minimal left ventricular pressure or volume overload they were within normal limits (–1±8 ms and 94±9 ms, respectively).

The following significant correlations were observed between early apex cardiographic relaxation time and internally measured indices of left ventricular performance: maximal rate of pressure fall (min dP/dt) in the left ventricle ($r=-0{\cdot}87$), velocity of lengthening of the contractile elements at minimum dP/dt ($r=-0{\cdot}83$), and ejection fraction ($r=-0{\cdot}80$); significant correlations with several other values of left ventricular function (end-diastolic pressure, maximal dP/dt, and peak measured velocity of shortening of the contractile elements) were also observed. In the total group of subjects total apex cardiographic relaxation time correlated significantly with early apex cardiographic relaxation time ($r=+0{\cdot}67$); further, in the catheterised patients total apex cardiographic relaxation time showed less close correlation with the internal indices.

The early and total relaxation time intervals in the left apex cardiogram are two important noninvasive methods for assessing left ventricular performance in man.

Evaluation of the left ventricular performance by noninvasive techniques is desirable, because conventional invasive methods are time consuming, expensive, and involve some risk for the patient. It has been shown that the apex cardiogram reflects left ventricular events accurately enough in a qualitative (Benchimol *et al.*, 1961; Epstein and Coulshed, 1973; Manolas *et al.*, 1975), and to some extent also quantitative fashion (Reale, 1967; Sutton *et al.*, 1970; Vetter *et al.*, 1972; Manolas *et al.*, 1974; Denef *et al.*, 1975; Manolas *et al.*, 1976; Manolas and Krayenbuehl, 1976). The use of amplitude parameters in the apex cardiogram has not been feasible because of their inherent dependence on thoracic shape and lack of generally accepted calibration methods. The significance of the time interval from the onset of the second heart sound to the protodiastolic nadir of the apex tracing for the identification of the opening snap in the phonocardiogram has been pointed out in the past by some authors (Legler *et al.*, 1963; Oriol *et al.*, 1965). Benchimol and Ellis (1967) first suggested

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that this time interval was identical with the isovolumic relaxation period and concluded that this interval might 'be a useful avenue to the study of the condition of left ventricular function in man'.

The present study was designed to assess the clinical value of relaxation time intervals measured from the apex cardiogram by simultaneous recording of its first derivative and the phonocardiogram by (1) defining the normal values of these intervals, (2) comparing patients with impaired left ventricular function with controls, (3) correlating the apex cardiographic relaxation intervals with internally measured indices of left ventricular performance, and (4) comparing these correlations with those of widely used isovolumic time measurements (Mason *et al.*, 1965; Spodick and Kumar, 1968) with the same haemodynamic indices.

Subjects and methods

SUBJECTS

Apex cardiograms were recorded in 119 subjects, all of whom had sinus rhythm. In 100 healthy individuals apex tracings alone were recorded, whereas in the other 19 subjects apex cardiograms were recorded during left heart catheterisation. The catheterised patients were premedicated with 10 mg chlordiazepoxide or 5 mg diazepam given orally one hour before the procedure. Informed consent was obtained from each person.

Group 1a

This group consisted of the 100 healthy volunteers with no cardiovascular abnormality as detected on physical examination, *x*-ray film, or electrocardiogram, in whom apex tracings alone were recorded in order to establish the normal range of the apex cardiographic relaxation time intervals and to evaluate the possible influence of the resting heart rate on them.

Group 1b

This group consisted of 8 patients without left heart valvular disease and without, or with only slight, pressure or volume overloading of the left ventricle; 3 patients had a small persistent ductus and 1 had a small ventricular septal defect (all 4 patients with a left-to-right shunt of less than 15% of the pulmonary flow). One patient had slight valvular pulmonary stenosis (peak pressure gradient 18 mmHg), 1 had a mild form of a coarctation of the aorta (peak pressure gradient 9 mmHg), 1 had a stenosis of the innominate artery, and 1 a functional murmur with paroxysmal supraventricular tachycardias. Left ventricular performance was determined by measuring the isovolumic indices at rest and during handgrip test (Krayenbuehl *et al.*, 1972, 1973) and was found to be within normal limits as was the ejection fraction in cineangiocardiogram of the left ventricle.

Group 2

This group consisted of 11 patients with non-obstructive cardiomyopathy and decreased left heart function at rest, as determined by the measurement of the isovolumic contractile indices and of the internal relaxation indices as well as by the ejection fraction; in most cases these patients showed an abnormal or pathological response on handgrip test (Krayenbuehl *et al.*, 1972, 1973). Four patients had, in addition, slight mitral regurgitation (less than 0·12 regurgitation fraction as measured by thermodilution method); 3 patients also had labile arterial hypertension, 1 had a small persistent ductus arteriosus, 1 had a ventricular septal defect (both with a left-to-right shunt of less than 15 per cent of the pulmonary flow), and 1 had slight aortic stenosis (mean systolic pressure gradient determined by planimetry 6 mmHg).

METHODS

Apex cardiograms were recorded with the subject in the left lateral decubitus position, usually at an angle of 20 to 40°; the pulse transducer was held by hand at the point of maximal impulse of the apex beat of the heart. In healthy persons of group 1a apex tracings were also recorded in different positions, both of the body as well as of the axis of of the transducer, and with variation of the pressure applied to the transducer in relation to the chest wall, in order to evaluate the possible effects of these factors on the relaxation time intervals of the apex cardiograms. The pulse transducer was constructed in our laboratory (Manolas *et al.*, 1975) and consisted of a Marey capsule (diameter 2 cm) with the interior surface of this capsule directly connected without air leakage (Kastor *et al.*, 1970) to a Bio-Tec-transducer (BT 250–T), which had a flat response at frequencies from 15 000 Hz down to 0 with an infinite time constant; the distance from the transducer to the opening of the capsule measured 0·7 cm. Because of its design this system had no measurable time delay (Piemme, 1963; Kesteloot *et al.*, 1969).

Left heart catheterisation was performed using the percutaneous transfemoral technique. Pressure curves were obtained from the left ventricle and the ascending aorta by Statham SF_1 or Millar catheter tipanometers but in some cases 8F pigtail catheters were used for the aortic tracings. The micro-manometers were introduced into the left ventricle by the retrograde or transseptal approach and into the ascending aorta by the retrograde route.

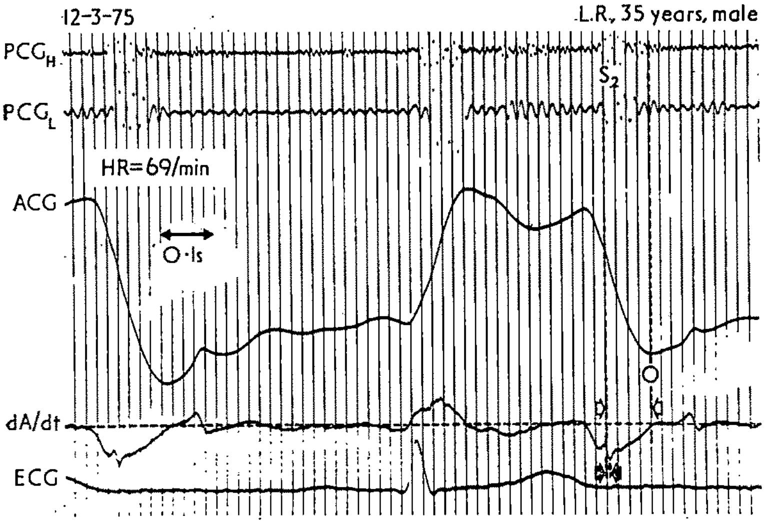

Fig. 1 *Normal subject: simultaneous records of left apex cardiogram (ACG), its first derivative (dA/dt), the external apical phonocardiogram (PCG_H = high frequencies, PCG_L = low frequencies), and lead II of the electrocardiogram (ECG). HR, heart rate. O, protodiastolic nadir of the apex cardiogram. S_2=onset of the aortic component of the second heart sound. Paper speed, 200 mm/s. The early apex cardiographic relaxation time (EART) is indicated by closed arrows; whereas the total apex cardiographic relaxation time (TART) is indicated by open arrows. For further explanation see text.*

Left ventriculography was carried out 40 to 70 minutes after recording the apex tracings. The patient was placed in the right anterior oblique position, and was told to hold his breath in mid-inspiration. Filming rate was 75 frames/s; 25 to 40 ml Urografin 76 per cent was delivered by an electrocardiograph-triggered power injector into the left ventricle at a rate of 10 to 15 ml/s. Further selective coronary arteriography was carried out using the Judkins technique. For the determination of ejection fraction the ventriculograms were viewed with a Tage-Arnø projector; by playing back and forth, the largest (end-diastolic) and the smallest (end-systolic) left ventricular silhouettes were identified and traced at the outermost endocardial border. Volumetric analysis was performed according to the area-length method (Dodge *et al.*, 1966), whereby in the end-diastolic and end-systolic silhouettes the long ventricular axis was drawn from the mitral-aortic junction to the apex. Ejection fraction (EF) was calculated according to the formula:

$$EF=\frac{A_S^2-L_D}{A_D^2-L_S}$$ where A_S is end-systolic and A_D is end-diastolic area, as determined by planimetry.

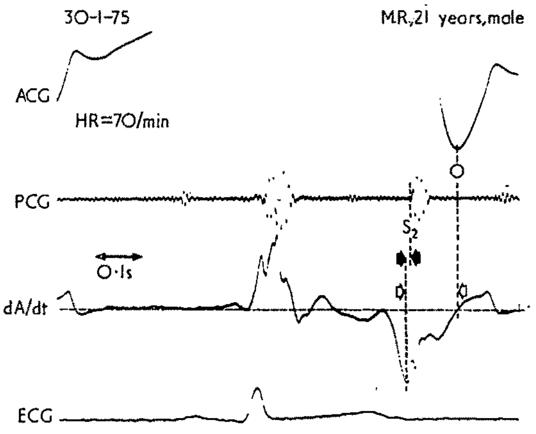

Fig. 2 *Definition of the apex cardiographic relaxation time intervals by the use of the first derivative of the apex cardiogram (as indicated also in Fig. 1), recorded for illustrative purposes with high amplification. Abbreviations as given in legend of Fig. 1. For explanation see text.*

ANALYSIS OF SIMULTANEOUS TRACINGS

All tracings were recorded on an 8- or 16-channel Electronics for Medicine oscillograph (DR-16) at a paper speed 200 mm/s, with time lines at 20 ms. In subjects of group 1a the apex cardiogram and its first derivative (dA/dt) were recorded simultaneously with the external apical phonocardiogram and lead II of the electrocardiogram (Fig. 1 and 2). In catheterised patients of groups 1b and 2 the following tracings (Fig. 3) were also recorded: the left ventricular pressure, its first derivative (dP/dt), and the instantaneous quotient of dP/dt to total left ventricular pressure (dP/dt)/P, the last two being obtained by use of an analogue computer. The time constant of the computer for calculating dP/dt and that of dA/dt was 0·8 ms, whereas that for calculating (dP/dt)/P was 1·1 ms. In addition (dP/dt)/P was calculated manually. The peak measured velocity of shortening of the contractile elements (V_{pm}) during the isovolumic phase of left ventri-

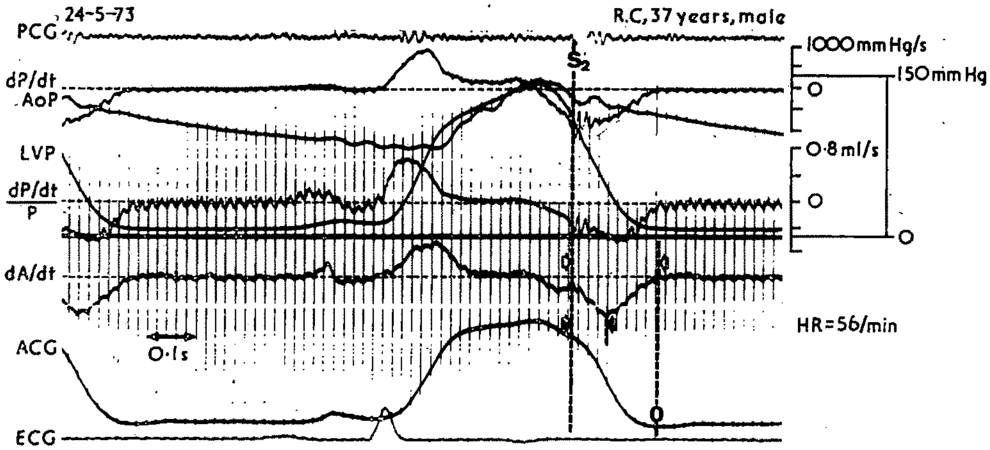

Fig. 3 *Simultaneous recordings of the left apex cardiogram (ACG), left ventricular pressure (LVP), and their derivatives (dA/dt and dP/dt, respectively), instantaneous velocity of shortening of the contractile elements [(dP/dt)/P], aortic pressure (AoP), the external apical phonocardiogram (PCG), and the electrocardiogram (ECG) from a patient with nonobstructive cardiomyopathy and decreased left ventricular function. Paper speed, 200 mm/s. The apex cardiographic relaxation values (indicated by arrows as in Fig. 1 and 2) are much prolonged (EART, 69 ms and TART, 178 ms).*

cular systole was calculated according to the formula:

V_{pm} in muscle lengths/s = max([dP/dt]/[P·28]) where 28 is the coefficient of series elasticity; similarly the velocity of lengthening of the contractile elements at min dP/dt was determined ([min dP/dt]/[P·28]), according to the value of (dP/dt)/(P·28) at the point of maximal pressure fall in the left ventricle, also in muscle lengths/s. The duration of the isovolumic phase of left ventricular systole was measured from the onset of the rise of the left ventricular pressure curve to the point of crossover of the left ventricle and aortic pressure curves. Measurements were also made of the time interval from the onset of left ventricular contraction to the peak of dP/dt (t–dP/dt).

Two relaxation time intervals were measured in the apex tracings: (1) the early apex cardiographic relaxation time, measured from the onset of the aortic component of the second heart sound (S_2) in the phonocardiogram to the negative peak of dA/dt, and (2) the total apex cardiographic relaxation time measured from S_2 to the protodiastolic nadir of the apex tracing, the latter being defined more accurately by determining the point where dA/dt after having reached its negative peak ascended and reached the zero line; this provides a more accurate temporal measurement of the protodiastolic nadir (0 point) of the apex tracing.

For each haemodynamic and apex cardiographic measurement 3 to 5 separate heart cycles were averaged.

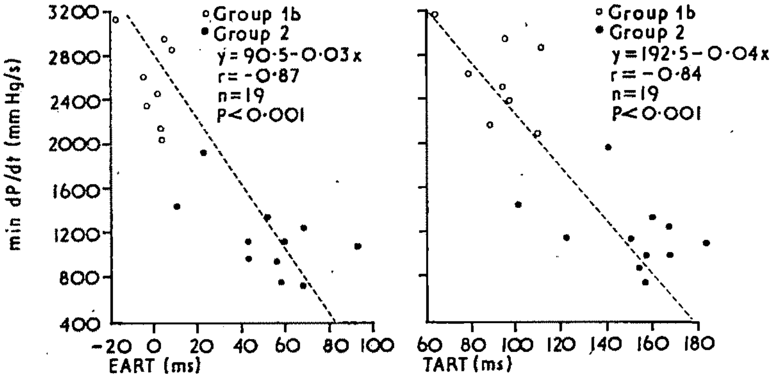

Fig. 4 *Linear regression analyses between maximal value of the left ventricular pressure fall (min dP/dt) and EART (left panel) and between min dP/dt and TART (right panel).*

Table 1 *Summary of patient data*

Case No.	*Age/Sex*	*Diagnosis*	*HR (min^{-1})*	*EART (ms)*	*TART (ms)*	*IVCT (ms)*	*t–dP/dt (ms)*	*AoP (mmHg)*	*LVP_{ac} (mmHg)*	*LVEDP (mmHg)*
Group 1b										
1	42 F	PS	76	+8	113	80	54	131/82	115	6/+3
2	19 F	PDA	83	+3	90	86	62	100/62	96	11/–
3	19 F	PDA	71	+2	95	51	49	97/64	90	12/+2
4	28 M	Coarc.	72	–3	99	80	59	129/83	108	7/0
5	33 F	STB	73	+5	96	73	64	141/88	133	11/0
6	21 M	PDA	64	+4	112	72	67	102/70	96	11/+3
7	29 M	FM	65	–18	65	80	67	182/109	142	12/–3
8	23 F	VSD	81	–5	81	89	66	106/77	88	6/–6
Mean	28		73	–1	94	76	61	124/79	109	10/0
±SD	8		7	8	9	12	7	29/15	20	4/3
Group 2										
9	37 M	CMP	56	+67	168	112	89	143/80	124	12/+8
10	54 M	CMP, AS	72	+60	154	102	89	124/91	145	31/+11
11	53 M	CMP, MR	66	+68	158	126	108	91/58	88	8/–1
12	62 M	CMP	59	+52	161	98	78	179/70	150	20/0
13	36 M	CMP, VSD	82	+10	101	74	67	113/74	85	18/+10
14	34 M	CMP	49	+56	157	76	67	107/62	94	22/+1
15	36 M	CMP	67	+43	123	87	75	165/99	146	50/+23
16	41 F	CMP	70	+43	167	109	88	98/64	79	10/+5
17	53 M	CMP	63	+58	155	115	90	104/68	94	10/+13
18	32 M	CMP, PDA	79	+22	144	97	77	176/84	121	10/–5
19	42 M	CMP	49	+93	185	76	72	153/102	138	32/+6
Mean	44		67	+52	152	97	82	132/77	115	20/+6
+SD	10		10	23	23	18	12	32/15	27	13/8
P	<0·001		NS	<0·001	<0·001	<0·01	<0·001	NS/NS	NS	NS/NS

AoP, aortic pressure; AS, aortic stenosis; CMP, nonobstructive cardiomyopathy; EART, early apex cardiographic relaxation time; TART, total apex cardiographic relaxation time; EF, ejection fraction; HR, heart rate; IVCT, isovolumic contraction time; LVEDP, left ventricular end-diastolic pressure (at rest/during handgrip; LVP_{ac}, left ventricular pressure at the level of the aortic closure; M, male; F, female; max dP/dt, maximal rate of rise of left ventricular pressure; MR, mitral regurgitation; min dP/dt, minimal rate of dP/dt; (min dP/dt)/(P·28) = velocity of lengthening of the contractile elements at min dP/dt; P, probability; PDA, persistent ductus arteriosus; t–dP/dt, time from the onset to peak dP/dt; V_{pm}, peak measured velocity of shortening of the contractile elements; VSD, ventricular septal defect; ML, muscle length. Listed are mean values ± SD. The P values were obtained by the unpaired Student's t test. NS, not significant (P > 0·05).

Results

Table 1 summarises the overall data obtained for haemodynamic, cineangiographic, and apex cardiographic measurements in the catheterised patients. The mean values of the following indices of left ventricular performance showed a significant difference at the level of $P < 0{\cdot}001$ in the two groups: the time from onset to the point of maximal rise of the left ventricular pressure (t-dP/dt), maximal rate of the left ventricular pressure rise (max dP/dt), maximal rate of pressure fall in the left ventricle (min dP/dt), peak measured velocity of shortening of the contractile elements (V_{pm}), and the velocity of lengthening of the contractile elements at min dP/dt ([min dP/dt]/[P·28_4]), as well as the ejection fraction; further, the isovolumic contraction time (IVCT) at $P < 0{\cdot}01$. Moreover, the age was significantly different ($P < 0{\cdot}001$) in these two groups. In contrast, there was no significant difference between groups 1b and 2 in the mean values of the heart rate, left ventricular end-diastolic pressure at rest and during handgrip test, systolic and diastolic aortic pressures, as well as the left ventricular pressure at the time of the aortic valve closure /LVP_{ac}).

Table 2 *Correlations between apex cardiographic relaxation parameters and internal indices of left ventricular performance*

	IVCT	*t-dP/dt*	*LVEDP*	*Max dP/dt*	*Min dP/dt*	*V_{pm}*	*$\frac{\text{Min dP/dt}}{\text{P·28}}$*	*EF*
EART	+0·55	+0·70	+0·47*	–0·65	–0·87	–0·70	–0·83	–0·80
TART	+0·57	+0·68	+0·31**	–0·62	–0·84	–0·62	–0·84	–0·75

P values were for all correlations <0·001, except *P < 0·01 and **NS. Abbreviations as in Table 1.

Max dP/dt (mmHg/s)	*Min dP/dt (mmHg/s)*	V_{pm} *(ml/s)*	*Min dP/dt* / *P·28* *(ml/s)*	*EF*
2100	2870	1·99	1·31	0·83
1360	2180	1·11	1·96	0·68
1560	2490	1·16	1·44	0·73
1920	2380	1·36	1·92	0·81
1740	2980	1·18	1·16	0·64
1400	2060	1·13	0·91	0·61
2110	3180	1·24	1·29	0·67
1350	2610	1·13	1·80	0·67
1580	1090	0·80	0·37	0·50
1690	2590	1·29	1·47	0·71
320	390	0·30	0·38	— 0·08
960	1220	0·72	0·52	0·44
840	1120	0·47	0·40	0·33
530	770	0·64	0·60	0·30
1120	1320	0·70	0·37	0·37
1040	1410	0·92	1·04	0·58
1080	990	0·74	0·48	0·40
1060	1110	0·42	0·35	0·32
770	980	0·66	0·42	0·40
720	780	0·72	0·36	0·32
1340	1980	0·93	0·71	0·52
1000	1160	0·69	0·51	0·41
290	340	0·15	0·20	0·09
< 0·001	< 0·001	< 0·001	< 0·001	< 0·001

Table 2 shows the correlation coefficients calculated by means of linear regression analyses for all catheterised patients using early or total apex cardiographic relaxation times as independent variables and indices derived from cardiac catheterisation data as dependent variables. Neither apex cardiographic relaxation time interval correlated significantly with LVP_{ac} or systolic and diastolic aortic pressures.

Early apex cardiographic relaxation time is defined as the interval between S_2 of the phonocardiogram and the negative peak of the first derivative of the apex tracing. This interval could not be measured in 20 per cent of the normals (group 1a) because of the presence of multiple peaks in the derivative tracing; in addition, early apex cardiographic relaxation time had negative values in 27 per cent of these subjects, because the negative peak of dA/dt preceded the onset of the aortic component of the second heart sound (Fig. 2). The value of the early apex cardiographic relaxation time was not, or was only slightly, influenced by differences in the position of the body as well as of the axis of the transducer and the extent of pressure to the transducer in relation to the thoracic wall. No significant linear correlation was present in the group 1a between early apex cardiographic relaxation time and resting heart rate ($r = -0{\cdot}16$, $P > 0{\cdot}1$) over a range from 49 to 118 beats/min as well as between early apex cardiographic relaxation time and the age ($r = +0{\cdot}18$, $P > 0{\cdot}05$) over a range from 17 to 50 years. Early apex cardiographic relaxation time in normal subjects averaged 3 ± 12 ms ranging from −24 to +20 ms; it was significantly ($P < 0{\cdot}001$) prolonged in group 2 (52 ± 23 ms), and within normal limits in group 1b (Table 1).

The relations between early apex cardiographic relaxation time and internally measured indices in the catheterised patients are given in Table 2. The highest degree of correlation was found with min dP/dt ($r = -0{\cdot}87$); and the correlation with ([min dP/dt]/[P·28]), EF and V_{pm} was very close to this. In contrast, the correlation with the isovolumic time indices (IVCT and d-dP/dt) as well as with left ventricular end-diastolic pressure was close.

Total apex cardiographic relaxation time is defined as the interval from S_2 of the phonocardiogram to the protodiastolic nadir of the apex cardiogram, where the latter is given at the point where the first derivative reaches the zero line after having reached its negative peak; using this method of timing total apex cardiographic relaxation time could always be measured. Total apex cardiographic relaxation time was significantly ($P < 0{\cdot}001$), but only very poorly, correlated with resting heart rate ($r = -0{\cdot}32$); less close, but also statistically significant ($P < 0{\cdot}01$), was the correlation with age ($r = +0{\cdot}30$). Total apex cardiographic relaxation time averaged 93 ± 16 ms in normal subjects, the range being from 63 to 123 ms; it was significantly prolonged ($P < 0{\cdot}001$) in group 2 (152 ± 23 ms). An identical significant inverse correlation was present, as shown in Table 1, between total apex cardiographic relaxation time and contractile relaxation indices (min dP/dt and [min dP/dt]/[P·28]) ($r = -0{\cdot}84$); the correlations with other haemodynamic and ventriculographic values was less close. In contrast, there was no significant correlation with left ventricular end-diastolic pressure. Total apex cardiographic relaxation time was significantly ($P < 0{\cdot}001$) correlated to early apex cardiographic relaxation time ($r = +0{\cdot}67$).

INTERNAL INDICES OF LEFT VENTRICULAR RELAXATION

The interrelation between internally measured relaxation values and other contractile as well as ventriculographic indices was also examined in the present study. The maximal rate of left ventricular pressure fall, called min dP/dt, showed an excellent correlation with max dP/dt ($r = +0{\cdot}93$); less close were the correlations with ejection fraction ($r = +0.88$) and with V_{pm} ($r = +0.83$); all these correlations were significant at $P < 0.001$. The velocity of lengthening of the contractile elements at min dP/dt, termed (min dP/dt)/(P·28), was significantly ($P < 0.001$) correlated with ejection fraction $r = +0.88$), V_{pm} ($r = +0.73$), and max dP/dt ($r = +0.63$).

INTERNAL TIME INDICES OF LEFT VENTRICULAR PERFORMANCE

In order to evaluate the relative importance of the noninvasively measured relaxation time indices derived from the apex tracing and the internally measured isovolumic time indices, linear regression analyses were performed using the latter as independent, and other indices of left ventricular performance as dependent variables.

The isovolumic contraction time correlated significantly ($P < 0.001$) with max dP/dt ($r = -0.69$) and ejection fraction ($r = -0.67$); in contrast, no significant correlation was observed with V_{pm} ($r = -0.25$, $P > 0.1$). The time from the onset to peak dP/dt, (t–dP/dt), showed the highest degree of correlation with ejection fraction ($r = -0.84$); it correlated less closely with max dP/dt ($r = -0.80$), but both correlations were significant at $P < 0.001$. There was no significant correlation between t–dP/dt and V_{pm} ($r = -0.28$, $P > 0.1$).

Discussion

In recent years temporal measurements derived from the apex cardiogram have been examined for their value in assessing left ventricular function by analysis of simultaneous recordings of the left apex cardiogram and left ventricular pressure in human subjects. First Reale (1967) and recently Vetter *et al.* (1972) studied the value of the first derivative of the apex cardiogram. More recently the value of the systolic upstroke time of the apex tracing has been established (Manolas *et al.*, 1976). The aim of this study was to compare relaxation time indices derived from the left apex tracing with other indices of cardiac performance derived from high fidelity left ventricular pressure curves and the cineangiocardiograms.

The experimental results of Cohn *et al.* (1972) in intact canine hearts showed 'the peak negative dP/dt to be a more reproducible measure of the rate of relaxation', and they concluded that negative dP/dt was related to the intrinsic contractility. Further, Hirzel *et al.* (1973) showed that min dP/dt was the measurement first affected after coronary occlusion in dogs. Investigation of the relaxation velocity of the contractile elements, as indicated by the quotient (dP/dt)/P, in ischaemic coronary disease was studied in this laboratory (Rutishauser *et al.*, 1971, 1973) and it was concluded that 'relaxation was more altered than contraction'. These observations accord with the findings in our present study that both min dP/dt and (min dP/dt)/ (P·28) correlate significantly with isovolumic contractile indices (max dP/dt and V_{pm}) as well as with the ejection fraction. Oriol *et al.* (1965) suggested 'a prediction of left atrial pressure from S_2–0 interval'. However, the value of the apex cardiographic relaxation for assessing left ventricular function was first pointed out by Benchimol and Ellis (1967) suggesting that the interval from the onset of the second heart sound to the 0 point (S_2–0) of the apex tracing was identical with the isovolumic relaxation time (IVRT) of the left ventricle; they found, from an excellent set of experiments, 'a decrease of IVRT during and after exercise' and that 'isoproterenol (isoprenaline) shortened IVRT', and concluded that there was 'no significant correlation between IVRT and age'. Recently Prewitt *et al.* (1975), comparing simultaneous recordings of echocardiogram and apex cardiogram found that 'the 0 point coincides neither with the initial nor with maximum opening of the mitral valve leaflets'; according to this finding the S_2–0 interval is not identical with the isovolumic relaxation time. In the present study we termed the S_2–0 interval 'total apex cardiographic relaxation time' where the 0 point of the apex tracing was defined more accurately by the use of the first derivative of the apex tracing (Fig. 1 and 2).

Our findings show that total apex cardiographic relaxation time was significantly prolonged in most patients with nonobstructive cardiomyopathy and decreased left ventricular performance (Table 1). Further, it was closely correlated with internally measured indices of relaxation and less closely but significantly with isovolumic contractile indices and the ejection fraction (Table 2). In contrast, there was only a weak correlation with the resting heart rate in normal subjects so that a rate correction is not necessary. No significant correlation was found between total apex cardiographic relaxation time and age in the normals; this contrasts with the findings of Harrison *et al.* (1964).

A new index of apex cardiographic relaxation is introduced in the present communication. The early apex cardiographic relaxation time was defined as the interval between the S_2 and the negative peak of dA/dt. Our findings show that the early apex cardiographic relaxation time can be measured in patients with a decreased rate of relaxation because of the presence of a sharp and single peaked negative wave in the first derivative of the apex cardiogram. The mean value of the early apex cardiographic relaxation time was significantly prolonged in the patients with non-obstructive cardiomyopathy and impaired left ventricular performance compared with the normal subjects. The most important finding in the present study consists in the close correlation between early apex cardiographic relaxation time and the invasively measured indices of the relaxation of the left ventricle; moreover, a close relation was present with the ejection fraction and with the isovolumic contractile indices (max dP/dt and Vxw). In contrast, there was no significant correlation between early apex cardiographic relaxation time and age in the group of normal subjects, thus agreeing with the findings of Benchimol and Ellis (1967). Furthermore, early qapex cardiographic relaxation time wa not significantly correlated with the resting heart rate. From these findings it can be concluded that the early apex cardiographic relaxation intervals are independent of these factors. Benchimol and Ellis (1967) pointed out that the 'isovolumic relaxation time' was dependent on three factors: (1) the rate of fall of left ventricular pressure, (2) the height of aortic or left ventricular pressure at the time of aortic valve closure, and (3) the height of left atrial pressure at the time of mitral opening. According to our findings in the present study both early and total apex cardiographic relaxation times showed no significant correlation with the left ventricular pressure at the time of aortic closure, or with systolic and diastolic aortic pressure; further, there was no significant difference in the mean values of these pressures between the two groups of the catheterised patients, which could account for the differences in the mean values of the apex cardiographic relaxation time intervals between group 1b and 2. Furthermore, the correlations between apex cardiographic relaxation time intervals and left ventricular end-diastolic pressure (Table 2) were poor. Thus, it would appear that these apex cardiographic intervals are influenced by changes of slope of the left ventricular pressure curve after the closure of the aortic valve.

Comparing the relative importance of early and total apex cardiographic relaxation times as indices of left ventricular performance, it should be noted (Table 2) that early apex cardiographic relaxation time showed closer correlations to internal relaxation and contractile indices as well as ejection fraction. In this context it must be emphasised that early apex cardiographic relaxation time showed no significant correlation with the resting heart rate, whereas total apex cardiographic relaxation time showed a poor though significant correlation. When one compares the apex cardiographic relaxation time intervals and the isovolumic contraction time in their relation to internal indices of left ventricular function, it is evident that the former correlate more closely to isovolumic contractile indices and ejection fraction than the latter, where the correlation between the isovolumic contraction time and V_{pm} was not significant. Mason *et al.* (1965) suggested the time to peak dP/dt as an excellent index of the contractile state of the left ventricle; according to our findings in this study this isovolumic time index of contraction showed a closer correlation with ejection fraction compared with the apex cardiographic relaxation intervals, but it was less closely correlated to max dP/dt and not significantly to V_{pm}. These data clearly show the superiority of early and total apex cardiographic relaxation times over other internally measured temporal indices of left ventricular function.

Conclusions

No single index of undisputed value for assessing left ventricular performance in man is available. Isovolumic contraction and relaxation indices derived from left ventricular pressure curves have been widely used. However, their use in repeated evaluation of patients with cardiac disease is limited since they require left heart catheterisation. This study has shown that two relaxation time values, derived from the left apex tracing, show good correlation with internal contractile indices and with the ejection fraction. The great value of these indices derived noninvasively is further enhanced because the measurement is inherently simple. However, the magnitude of the correlation coefficients does not permit one to estimate with sufficient confidence in an individual subject the corresponding invasive indices of relaxation or the ejection fraction on the basis of the noninvasive measurements discussed above. It should also be noted that this study establishes the usefulness of the apex cardiographic relaxation times for the assessment of interpatient differences of basal contractile state in subjects without or with only a slight volume or pressure overload. The validity of early and total apex cardiographic relaxation time intervals for assessing changes in the inotropic state of the left ventricle as well as in the presence of moderate or severe valvular disease requires further investigation.

References

Benchimol, A., Dimond, E. G., and Carson, J. C. (1961). The value of the apex cardiogram as reference tracing in phonocardiography. *American Heart Journal*, **61**, 485–493.

Benchimol, A., and Ellis, J. G. (1967). A study of the period of isovolumic relaxation in normal subjects and in patients with heart disease. *American Journal of Cardiology,* **19,** 196–206.

Cohn, P. F., Liedtke, A. J., Serur, J., Sonnenblick, E. H., and Urschel, C. W. (1972). Maximal rate of pressure fall (peak negative dP/dt) during ventricular relaxation. *Cardiovascular Research,* **6,** 263–267.

Denef, B., Popeye, R., De Geest, H., and Kesteloot, H. (1975). On the clinical value of calibrated displacement apexcardiography. *Circulation,* **51,** 541–551.

Dodge, H. T., Sandler, H., Baxley, W. A., and Hawley, R. R. (1966). Usefulness and limitations of radiographic methods for determining left ventricular volume. *American Journal of Cardiology,* **18,** 10–24.

Epstein, E. J., and Coulshed, N. (1973). Phonocardiogram and apex cardiogram in systolic click-late systolic murmur syndrome. *British Heart Journal,* **35,** 260–275.

Harrison, T. R., Dixon, K., Russell, R. O., Jr., Bidwai, P. S., and Coleman, H. N. (1964). The relation of age to duration of contraction, ejection, and relaxation of the normal human heart. *American Heart Journal,* **67,** 189–199.

Hirzel, H. O., Meier, W., Krayenbuehl, H. P., and Mehmel, H. (1973). Left ventricular dynamics during acute ischemia in the dog. In *Coronary Heart Disease, 2nd International Symposium, Frankfurt,* 1972, p. 156. Ed. by M. Kaltenbach, P. Lichtlen, and G. C. Friesinger., Thieme, Stuttgart.

Kastor, J. A., Aronow, S., Nagle, R. E., Garber, T., and Walker, H. (1970). Air leaks as a source of distortion in apexcardiography. *Chest,* **57,** 163–171.

Kesteloot, H., Willems, J., and Van Vollenhoven, E. (1969). On the physical principles and methodology of mechanocardiography. *Acta Cardiologica,* **24,** 147–160.

Krayenbuehl, H. P., Rutishuser, W., Schoenbeck, M., and Amende, I. (1972). Evaluation of left ventricular function from isovolumic pressure measurements during isometric exercise. *American Journal of Cardiology,* **29,** 323–330.

Krayenbuehl, H. P., Rutishauser, W., Wirz, P., Amende, I., and Mehmel, H. (1973). High-fidelity left ventricular pressure measurements for the assessment of cardiac contractility in man. *American Journal of Cardiology,* **31,** 415–427.

Legler, J. F., Benchimol, A., and Dimond, E. G. (1963). The apex cardiogram in the study of the 2–OS interval. *British Heart Journal,* **25,** 246–250.

Manolas, J., and Krayenbuehl, H. P. (1976). Assessment of left ventricular function in aortic incompetence by the systolic upstroke time of the apexcardiogram. (Abstract.) *Circulation,* **53-54,** Suppl. II, 60.

Manolas, J., Rutishauser, W., Wirz, P., and Arbenz, U. (1975). Time relation between apex cardiogram and left ventricular events using simultaneous high-fidelity tracings in man. *British Heart Journal,* **37,** 1263–1267.

Manolas, J., Wirz, P., Krayenbuehl, H. P., and Rutishauser, W. (1974). Kontraktilitätskriterien am simultan mit dem linksventrikulären Druck registrierten, frequenz- und amplitudengetreuen Apexkardiogramm. *Schweizerische medizinische Wochenschrift,* **104,** 1590–1592.

Manolas, J., Wirz, P., and Rutishauser, W. (1976). Relationship between duration of systolic upstroke of apexcardiogram and internal indexes of myocardial function in man. *American Heart Journal,* **91,** 726–734.

Mason, D. T., Sonnenblick, E. H., Ross, J., Jr., Covell, J. W., and Braunwald, E. (1965). Time to peak dP/dt: a useful measurement for evaluating the contractile state of the human heart (abstract). *Circulation,* **31-32,** Suppl. II, **145.**

Oriol, A., Palmer, W. H., Nakhjaran, F., and McGregor, M. (1965). Prediction of left atrial pressure from the second sound-opening snap interval. *American Journal of Cardiology,* **16,** 184–188.

Piemme, T. E. (1963). Pressure measurement: electrical pressure transducers. *Progress in Cardiovascular Diseases,* **5,** 574–594.

Prewitt, T., Gibson, D., Brown, D., and Sutton, G. (1975). The 'rapid filling wave' of the apex cardiogram. Its relation to echocardiographic and cineangiographic measurements of ventricular filling. *British Heart Journal,* **37,** 1256–1262.

Reale, A. (1967). Evaluation of the contractile state of the human heart from the first derivative of the apexcardiogram. *Circulation,* **36,** 933–941.

Rutishauser, W., Amende, I., and Krayenbuehl, H. P. (1973). Course of relaxation of the left ventricle during stress tests in coronary disease. In *Das chronisch kranke Herz,* p. 341. Ed. by H. Roskamm and H. Reindell. Schaffauer Verlag, Stuttgart and New York.

Rutishauser, W., Amende, I., and Schoenbeck, M. (1971). Relaxation velocity of contractile elements in ischemic coronary heart disease. (Abstract.) *Circulation,* **43-44,** Suppl. II, 220.

Spodick, D. H., and Kumar, S. (1968). Isovolumetric contraction period of the left ventricle. Results in a normal series and comparison of methods of calculation by atraumatic techniques. *American Heart Journal,* **76,** 498–503.

Sutton, G. C., Prewitt, T. A., and Craige, E. (1970). Relationship between quantitated precordial movement and left ventricular function. *Circulation,* **41,** 179–190.

Vetter, W. R., Sullivan, R. W., and Hyatt, K. H. (1972). Assessment of quantitative apex cardiography. A noninvasive index of left ventricular function. *American Journal of Cardiology,* **29,** 667–671.

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Enzymic analysis of endomyocardial biopsy specimens from patients with cardiomyopathies

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Myocardial biopsies have been obtained from patients with hypertrophic or congestive cardiomyopathies. Marker enzymes for the principal subcellular organelles of the myocardium were estimated using highly sensitive assay procedures. The results were compared with those obtained in tissue from patients with valvular heart disease with good or poor left ventricular function.

Left ventricular myocardial tissue from patients with hypertrophic cardiomyopathy showed essentially normal levels of enzymic activities.

In congestive cardiomyopathy, right ventricular tissue showed reduced levels of mitochondrial enzymes with increased levels of lactate dehydrogenase.

Left ventricular tissue from patients with congestive cardiomyopathy showed reduced levels of mitochondrial and myofibril enzymes but high levels of lactate dehydrogenase. The reduced levels of myofibril Ca^{++}*-activated ATP in congestive cardiomyopathy is similar to that found in patients with impaired left ventricular function secondary to valvular disease.*

It is suggested that defective mitochondrial function is a characteristic feature of congestive cardiomyopathy and that the increased levels of lactate dehydrogenase reflect a compensatory response.

Although extensively studied both by the examination of postmortem tissue and by clinical studies, little is known of the underlying nature of the group of diseases known as the primary cardiomyopathies. On clinical criteria two main subgroups have been distinguished (Goodwin and Oakley, 1972). The hypertrophic cardiomyopathies form a distinct clinical and pathological entity. Bands of hypertrophied muscle are present which may obstruct the outflow tract of either ventricle, though the left ventricle is more commonly affected than the right. Histologically this tissue shows a characteristic pattern of muscle fibre arrangement but the remainder of the myocardium is essentially normal (Maron *et al.*, 1975). The congestive cardiomyopathies form a heterogeneous group of diseases, usually of unknown aetiology but sometimes due to viruses or toxins, such as ethanol, with similar clinical and pathological features (Goodwin and Oakley, 1972).

The introduction of the bioptome has provided a safe and reliable method of obtaining endomyocardial tissue from both the left and right ventricles (Konno *et al.*, 1971; Brooksby *et al.*, 1974). Examination of the tissue by morphological techniques can provide information of diagnostic value (Olsen, 1974) but these studies have thrown little light on the mechanism of the myocardial damage. The use of enzymic analysis of milligram quantities of tissue has proved of value in the understanding of certain experimental diseases of the cardiovascular system in animals (Peters *et al.*, 1972; Peters and de Duve, 1974; Welman and Peters, 1976, 1977). The application of a similar approach to various human diseases has similarly proved rewarding (Kane and Peters, 1975; Peters *et al.*, 1975; Peters and Seymour, 1976; Segal and Peters, 1976). In the present paper this approach is applied to tissue obtained by endomyocardial biopsy from patients with cardiomyopathy, in an attempt to gain insight into the disease processes in this group of disorders.

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Subjects and methods

SUBJECTS

Patients with cardiomyopathies or with valvular heart disease secondary to either previous rheumatic fever or to bacterial endocarditis were investigated by routine diagnostic catheterisation.

The patients were assigned to the various diagnostic groups after reviewing the clinical features, catheter studies, and histological data. Left ventricular function was assessed as described previously (Peters *et al.*, 1976) and left ventricular biopsies were obtained by the technique of Brooksby *et al.* (1974) at St. Thomas' Hospital. Right ventricular biopsies were obtained with the Olympus bioptome by a modification of Konno's method (Konno *et al.*, 1971) at Hammersmith Hospital. The material was processed by conventional techniques for both light and electron microscopy. A separate biopsy for enzymic analysis was immediately placed in ice-cold 0·25 mol/l sucrose containing 1 mmol/l Na_2 EDTA *p*H 7·2 and stored at –20° until assay. The investigations reported in this publication have been approved by the relevant ethical committees.

ENZYMIC ANALYSES

Because of the small size of the biopsies, approximately 5 mg, highly sensitive enzyme assays using fluorigenic and radio-labelled substrates have been employed (Peters *et al.*, 1972). The tissue was homogenised in 2 ml isotonic sucrose with 10 strokes of a tight fitting pestle (type B) in a Dounce homogeniser (Kontes Glass Co., Vineland, N.J., U.S.A.). A single biopsy was assayed, in duplicate, from each patient. Table 1 shows the assay procedure used for the principal marker enzymes. In order to assess the optimum *p*H, optimal assay conditions, linear kinetics with respect to time of incubation, and amount of enzyme and variability of assay procedures (Seymour and Peters, 1977), preliminary studies were made for each enzyme with material obtained at the time of open heart surgery.

Ca^{++}-activated ATPase was assayed with $\gamma[^{32}P]$ ATP as described by Avruch and Wallach (1971). The incubation medium contained 2 mmol/l ATP, 10 mmol/l Ca^{++}, 100 mmol/l Tris-HCl buffer, *p*H 7·4 in a total volume of 0·5 ml. After incubation for up to 30 minutes at 37°C the reaction was stopped by the addition of 1 ml of solution containing 4 per cent activated charcoal and 4 per cent celite in 0·1 mol/l HCl containing 10 mmol/l NaH_2PO_4. After standing for 30 minutes at 0°C the mixture was centrifuged at 2000 g for 20 minutes. 0·5 ml of the supernatant was mixed with 10 ml Triton-toluene scintillant (Lazarow and de Duve, 1971). Appropriate blanks and standards were assayed with all samples. Corrections for basal ATPase activity were made by parallel assays in which the calcium ions were replaced by 1 mmol/l EDTA. In order to enhance the specificity of the Ca^{++}-activated ATPase for the myofibrillary component, assays were performed in which 10 mmol/l sodium azide or 0·1 mmol/l oligomycin was added to the incubation medium. These compounds are selective inhibitors of mitochondrial ATPase activity (Fanbury and Gergely, 1965; Harigaya and Schwartz, 1969; Bloomfield and Peters, 1974; Leclercq and Swynghedauw, 1976). Enzyme activity associated with the myofibrils (Chandler *et al.*, 1967) and with the sarcolemma (Bloomfield and Peters, 1974) are relatively unaffected.

Enzyme activities were expressed as milliunits of activity/mg protein where 1 milliunit corresponds to the hydrolysis of 1 nmol substrate. Protein was

Table 1 *Enzyme assay conditions*

Enzyme	*Substrate*	*pH*	*Incubation medium*	*Reference*
Lactate dehydrogenase	Pyruvate; NADH	7·4	0·1 mol/l sodium phosphate buffer*; 1 mmol/l dithiothreitol	Reeves and Fimognari (1966); Lowry *et al.* (1957)
Malate dehydrogenase	Oxaloacetate; NADH	7·4	0·1 mol/l sodium phosphate buffer*; 1 mmol/l dithiothreitol	Dupourque and Kun (1969); Lowry *et al.* (1957)
Glutamate dehydrogenase	α-ketoglutarate, NADH $(NH_4)_2SO_4$	7·4	0·07 mol/l triethanolamine-HCl buffer*	Ellis and Goldberg (1972); Lowry *et al.* (1957)
Monoamine oxidase	^{14}C tryptamine	7·4	0·3 mol/l Na phosphate buffer	Wurtman and Axelrod (1963)
5′ Nucleotidase	$[^3H]$adenosine 5′ monophosphate	9·0	60 mmol/l piperazine-HCl buffer 24 mmol/l $MgCl_2$; 12 mmol/l 2-glycerophosphate	Seymour and Peters (1977)
α-glucosidase	4-methylumbelliferyl α-glucopyranoside	7·5	0·1 mol/l sodium acetate buffer†	Peters *et al.* (1972)
Acid phosphatase	4-methylumbelliferyl phosphate	4·0	0·1 mol/l sodium acetate buffer†	Peters *et al.* (1972)
N-acetyl-β-glucosaminidase	4-methylumbelliferyl-2-acetamide-2-deoxy-β-D-glucopyranoside	5·8	0·1 mol/l sodium acetate buffer	Peters *et al.* (1972)
β-glucuronidase	4-methylumbelliferyl-β-D-glucuronide trihydrate	3·5	0·1 mol/l sodium acetate buffer†	Peters *et al.* (1972)
Cathepsin D	$[^{14}C]$-cyanate labelled haemoglobin	3·5	0·1 mol/l sodium acetate buffer†	Roth *et al.* (1971)

*Incubation medium contained 0·01 per cent Triton × 100.
†Incubation medium contained 0·1 per cent Triton × 100.

assayed by the method of Lowry *et al.* (1951) with bovine serum albumin as standard.

DNA was assayed by the fluorometric technique of Le Pecq and Paoletti (1966) with calf thymus DNA (Sigma) as standard.

Results

HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY

Table 2 shows specific activities of marker enzymes in the cardiac biopsies from patients with hypertrophic cardiomyopathy and from patients previously reported (Peters *et al.*, 1976) with valvular heart disease with good left ventricular function. The levels of the enzymes in the myopathic tissue were consistently higher than in the valvular heart disease tissue, though this increase only reaches statistical significance for three enzymes. The azide-resistant Ca^{++}-activated ATPase was significantly higher in the myopathic tissue though the total Ca^{++}-activated ATPase failed to reach a statistically significant increase. Malate and lactate dehydrogenases were significantly different between the two groups. For the other marker enzymes there was no difference between the two patient categories.

A limited number of preliminary experiments have been performed in which tissue obtained at open heart surgery, from patients with hypertrophic obstructive cardiomyopathy, was assayed for marker enzyme activities and the levels compared with left ventricular tissue from patients with congenital or acquired valve disease also obtained at open heart surgery. Though the specific activities of the enzymes in the tissue obtained by open biopsy were higher than those in tissue obtained by endomyocardial biopsy, the mitochondrial and myofibril marker enzyme activities were higher in the hypertrophic cardiomyopathy tissue than in the valvular heart disease tissue.

CONGESTIVE CARDIOMYOPATHY

Table 3 compares the specific enzyme activities in left ventricular muscle from the congestive cardiomyopathy patients and the two valvular heart disease groups. The levels of Ca^{++}–ATPase activity in the myopathic group were intermediate between the two valvular heart disease groups whether assayed in the presence or absence of azide. The levels of lactate dehydrogenase in the congestive cardiomyopathy tissue were significantly raised compared with both the control groups. Malate and glutamate dehydrogenases, however, were present at lower concentrations in the myopathic group than in the control tissue. Monoamine oxidase, 5′ nucleotidase, α-glucosidase, the acid hydrolases, and DNA content of the tissue were not significantly different between any of the patient groups.

Table 4 shows the results of assays of marker enzymes in right ventricular biopsies from valvular heart disease and myopathic patients. The pattern of results is similar to that found with the left ventricu-

Table 2 *Enzymic analysis of left ventricular biopsies (mean ± SEM milliunits/mg protein; number of samples assayed between parentheses)*

Enzyme	*Valvular heart disease* with good LV function*	*Hypertrophic cardiomyopathy*	*Statistical significance*
Ca^{++}-dependent ATPase	48·9 ±4·6 (16)	62·1 ±8·4 (10)	$P < 0·05$
Oligomycin-insensitive Ca^{++}-dependent ATPase	40·4 ±4·0 (15)	50·4 ±13·6 (4)	$P > 0·05$
Azide-insensitive Ca^{++}-dependent ATPase	42·1 ±4·8 (12)	57·0 ±8·7 (5)	$P < 0·05$
Lactate dehydrogenase	232 ±35 (23)	395 ±58 (12)	$P < 0·025$
Malate dehydrogenase	4250 ±290 (20)	5880 ±150 (11)	$P < 0·005$
Glutamate dehydrogenase	6·24 ±1·34 (21)	7·95 ±1·99 (5)	$P > 0·05$
Monoamine oxidase	1·41 ±0·56 (13)	2·42 ±0·45 (13)	$P > 0·05$
5′ Nucleotidase	10·9 ±2·25 (16)	11·9 ±1·3 (10)	$P > 0·05$
Neutral α-glucosidase	0·043 ±0·010 (11)	0·176 ±0·037 (9)	$P > 0·05$
Acid phosphatase	1·71 ±0·34 (14)	2·92 ±0·51 (8)	$P > 0·05$
N-acetyl-β-glucosaminidase	1·050 ±0·35 (13)	1·99 ±0·33 (11)	$P > 0·05$

*Peters *et al.* (1976).

lar biopsies with significantly reduced levels of Ca^{++}-dependent ATPase and glutamate and malate dehydrogenase but with much increased levels of lactate dehydrogenase. The levels of monoamine oxidase and the acid and neutral hydrolases were not significantly different between the two groups.

Discussion

The data in this paper represent the first attempt to investigate the subcellular pathology with biochemical techniques in the myopathic human heart using endomycardial biopsy material. Certain

Table 3 *Enzymic analysis of left ventricular biopsies (mean ± SEM milliunits/mg protem number of samples assayed between parentheses)*

Enzyme	*Valvular heart disease**		*Congestive*	*Statistical significance*	
	Good function (G)	*Poor function (P)*	*cardiomyopathy*	*G*	*P*
Ca^{++}-activated ATPase	48·9 ±4·6 (16)	23·4 ±4·4 (16)	28·6 ±2·9 (8)	$P<0·05$	$P>0·05$
Azide-insensitive Ca^{++}-activated ATPase	42·1 ±4·8 (12)	10·4 ±1·9 (15)	20·4 ±4·9 (7)	$P<0·05$	$P<0·05$
Lactate dehydrogenase	232 ±35 (23)	421 ±58 (20)	1390 ±300 (8)	$P<0·005$	$P<0·01$
Malate dehydrogenase	4250 ±290 (20)	3110 ±350 (18)	1320 ±190 (8)	$P<0·0005$	$P<0·01$
Glutamate dehydrogenase	6·24 ±1·3 (21)	4·25 ±1·51 (14)	1·62 ±0·31 (6)	$P<0·05$	$P>0·05$
Monoamine oxidase	1·41 ±0·56 (13)	2·37 ±0·58 (15)	1·42 ±0·06 (5)	$P>0·05$	$P>0·05$
5′ Nucleotidase	10·9 ±2·25 (16)	9·76 ±1·93 (14)	8·89 ±2·1 (7)	$P>0·05$	$P>0·05$
Neutral α-glucosidase	0·043 ±0·010 (11)	0·053 ±0·010 (9)	0·050 ±0·021 (7)	$P>0·05$	$P>0·05$
Acid phosphatase	1·71 ±0·31 (14)	1·61 ±0·30 (12)	2·01 ±0·51 (8)	$P>0·05$	$P>0·05$
N-Acetyl-β-glucosaminidase	1·05 ±0·35 (13)	0·734 ±0·103 (16)	0·99 ±0·21 (7)	$P>0·05$	$P>0·05$
Cathepsin D	74·5 ±13·0 (10)	59·2 ±8·7 (8)	49·9 ±13·2 (5)	$P>0·05$	$P<0·05$
β-glucuronidase	1·09 ±0·26 (5)	0·91 ±0·37 (7)	0·819 ±0·27 (4)	$P>0·05$	$P>0·05$
DNA	18·0 ±1·64 (13)	16·4 ±2·7 (8)	17·0 ±4·2 (7)	$P>0·05$	$P>0·05$

*Peters *et al.* (1976).

Table 4 *Enzymic analysis of right ventricular biopsies (mean ± SEM milliunits of activity/mg protein; number of samples assayed between parentheses)*

Enzyme	*Valvular heart disease**	*Congestive cardiomyopathy*	*Statistical significance*
Ca^{++}-dependent ATPase	39·9 ±4·1 (8)	20·8 ±4·9 (8)	$P<0·05$
Lactate dehydrogenase	336 ±69 (10)	1530 ±260 (8)	$P<0·005$
Malate dehydrogenase	4030 ±106 (8)	2540 ±700 (8)	$P<0·01$
Glutamate dehydrogenase	4·50 ±0·20 (7)	1·04 ±0·04 (8)	$P<0·05$
Monoamine oxidase	3·78 ±0·83 (8)	2·08 ±0·54 (8)	$P>0·05$
5′ Nucleotidase	8·10 ±1·12 (8)	6·10 ±1·21 (9)	$P>0·05$
Neutral α-glucosidase	0·073 ±0·019 (8)	0·078 ±0·020 (9)	$P>0·05$
Acid phosphatase	2·39 ±0·32 (8)	2·00 ±0·32 (9)	$P>0·05$
N-acetyl-β-glucosaminidase	0·49 ±0·12 (10)	0·71 ±0·12 (8)	$P>0·05$

*Peters *et al.* (1976).

technical problems had to be overcome before these studies could be undertaken. Because of the small size of the tissue fragments obtained and the large number of different marker enzymes to be assayed, highly sensitive techniques using fluorigenic and radiolabelled substrates were necessary. The variation between duplicate estimations was within 5 per cent but the variation between separate biopsies from the same patient could be up to 20 per cent. This variability is the result of the different amounts of endocardium and myocardium in the individual biopsies. This fact, together with the wide scatter of results in the patient groups and the technical difficulties in the measurements, makes the routine use of these estimations in the diagnosis of cardiomyopathy unlikely. Nevertheless, by comparing pooled data from groups of patients, it is hoped that clues to the pathogenesis of the disease could be obtained.

One problem encountered in the present work and common to most biochemical studies on tissue fragments is the nature of the reference used in expressing the results. In the present study the enzyme activities have been expressed in terms of total tissue protein. Analysis of the DNA content of tissues from valvular heart disease and myopathic heart disease indicates no significant differences in the DNA/protein ratio, suggesting that enzyme changes per cell are similar to the changes per mg protein. The use of wet or dry tissue weights as reference indices is not practicable.

The finding of increased levels of enzymes associated with the myofibrils in patients with hypertrophic cardiomyopathy may be associated with the histological findings of grossly hypertrophied and irregularly arranged myocardial fibres (Maron *et al.*, 1975). The increased myofibril ATPase activity is probably a reflection of hypertrophy without cardiac failure (Thyrum *et al.*, 1971). The increased levels of certain mitochondrial enzyme activities presumably reflect the increased energy requirements of the hypertrophic tissue. Morphological studies have commented on the increased numbers of this organelle, 'mitochondriosis' in the myocardium in hypertrophic cardiomyopathy (van Noorden *et al.*, 1971; Sekiguchi, 1974). However, the enzyme which shows the greatest increase, malate dehydrogenase, also has a significant localisation to the cytosol of the myocardium, and it is not clear in which of these components it is increased. Increased numbers of lipofuscin-containing bodies, presumed to be lysosomes, have been described in hypertrophic cardiomyopathy (van Noorden *et al.*, 1971). Though the two lysosomal enzymes, acid phosphatase and N-acetyl-β-glucosaminidase, assayed in the present studies were raised compared with the control tissue, the difference did not reach statistical significance. These studies do not, therefore, indicate a pronounced defect in any of the organelles of the myocardial cell in hypertrophic cardiomyopathy.

The studies on the tissue from the patients with congestive cardiomyopathy do show abnormalities in the levels of certain marker enzymes. The levels of myofibril associated Ca^{++}-dependent ATPase are reduced, but it is likely that this is associated with impaired ventricular function (Berson and Swynghedauw, 1973; Conway *et al.*, 1975; Peters *et al.*, 1976). The decreased levels of mitochondrial enzymes, particularly those associated with the inner mitochondrial matrix, are of interest. It is unlikely that this simply reflects a reduction in the total number of mitochondria, as monoamine oxidase, associated with the outer mitochondrial membrane (Schnaitman and Greenawalt, 1968; Parsons *et al.*, 1966), is not significantly altered. Electron microscopical examination of the myocardium from patients with congestive cardiomyopathy has disclosed increased numbers of mitochondria, many of which show cristolysis (Olsen, 1975). The present studies suggest an abnormality in the properties or function of mitochondria in tissue from patients with congestive cardiomyopathy. Studies in the strain of Syrian hamster which suffers from a hereditary cardiomyopathy have also shown mitochondrial abnormalities (Sordahl *et al.*, 1972). Similarly, experiments on myopathic tissue obtained from a transplant recipient have also indicated abnormalities in the properties of the mitochondria (Sordhal *et al.*, 1972; Schwartz *et al.*, 1973).

The increased levels of lactate dehydrogenase in the congestive cardiomyopathy tissue from both left and right ventricle are striking. This increased enzyme activity may be the result of the impaired mitochondrial function. Difficulty in producing sufficient ATP by aerobic glycolysis leads to enhanced anaerobic glycolysis which would be associated with increased lactate dehydrogenase levels in the tissue. This has been clearly shown in experimental animals (Yang, 1963; Williamson, 1966; Bishop and Altschuld, 1971). In patients with cardiomyopathy, lactate production, rather than lactate extraction, can be shown even in the presence of normal blood flow (Brachfeld, 1974). It would be of considerable interest to assay certain of the intermediates of carbohydrate metabolism in tissue from patients with congestive cardiomyopathy in an attempt to clarify the possible defects in mitochondrial function.

The levels of enzymes associated with the other cell organelles, viz. sarcolemma (5′ nucleotidase), lysosomes, (acid phosphatase, N-acetyl- β-glucosaminidase, β-glucuronidase, cathepsin D), and endoplasmic reticulum (α-glucosidase) are not significantly different in the two patient groups whether left or right ventricles are studied. It is, therefore, unlikely that any major defect in the functions of these organelles occurs in the cardiomyopathies.

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References

Avruch, J., and Wallach, D. F. H. (1971). Preparation and properties of plasma membrane and endoplasmic reticulum fragments from isolated rat fat cells. *Biochimica et Biophysica Acta,* **233,** 334–347.

Berson, G., and Swynghedauw, B. (1973). Cardiac myofibrillar ATPase and electrophoretic pattern in experimental heart failure produced by a two-step mechanical overloading in the rat. *Cardiovascular Research,* **7,** 464–469.

Bishop, S. P., and Altschuld, R. A. (1971). Evidence for increased glycolytic metabolism in cardiac hypertrophy and congestive heart failure. In *Cardiac Hypertrophy,* p. 567. Ed. by N. R. Alpert. Academic Press, New York.

Bloomfield, F. J., and Peters, T. J. (1974). Analytical subcellular fractionation of guinea pig myocardium with special reference to the localization of the adenosine triphosphatases. *Biochemical Society Transactions,* **2,** 1098–1101.

Brachfeld, N. (1974). Ischemic myocardial metabolism and cell necrosis. *Bulletin of the New York Academy of Medicine,* **50,** 261–293.

Brooksby, I. A. B., Jenkins, B. S., Coltart, D. J., Webb-Peploe, M. M., and Davies, M. J. (1974). Left ventricular endomyocardial biopsy. *Lancet,* **2,** 1222–1225.

Chandler, B. M., Sonnenblick, E. H., Spann, J. F., and Pool, P. E. (1967). Association of depressed myofibrillar adenosine triphosphatase and reduced contractility in experimental heart failure. *Circulation Research,* **21,** 717–725.

Conway, G., Heazlitt, R. A., Montag, J., and Mattingley, S. F. (1975). The ATPase activity of cardiac myosin from failing and hypertrophied hearts. *Journal of Molecular and Cellular Cardiology,* **7,** 817–826.

Dupourque, D., and Kun, E. (1969). Cytoplasmic and mitochondrial malate dehydrogenases from beef kidney. *Methods in Enzymology,* **13,** 116–122.

Ellis, G., and Goldberg, D. M. (1972). Optimal conditions for the kinetic assay of serum glutamate dehydrogenase activity at 37°C. *Clinical Chemistry,* **18,** 523–527.

Fanburg, B., and Gergely, J. (1965). Studies on adenosine triphosphate-supported calcium accumulation by cardiac subcellular particles. *Journal of Biological Chemistry,* **240,** 2721–2728.

Goodwin, J. F., and Oakley, C. M. (1972). The cardiomyopathies. *British Heart Journal,* **34,** 545–552.

Harigaya, S., and Schwartz, A. (1969). Rate of calcium binding and uptake in normal animal and failing human cardiac muscle. *Circulation Research,* **25,** 781–794.

Kane, S. P., and Peters, T. J. (1975). Analytical subcellular fractionation of human granulocytes with reference to the localization of vitamin B_{12}-binding proteins. *Clinical Science and Molecular Medicine,* **49,** 171–182.

Konno, S., Sekiguchi, M., and Sakakibara, S. (1971). Catheter biopsy of the heart. *Radiologic Clinics of North America,* **9,** 491–510.

Lazarow, P. B., and de Duve, C. (1971). Intermediates in the biosynthesis of peroxisomal catalase in rat liver. *Biochemical and Biophysical Research Communications,* **45,** 1198–1204.

Leclercq, J. F., and Swynghedauw, B. (1976). Myofibrillar ATPase, DNA and hydroxyproline content of human hypertrophied heart. *European Journal of Clinical Investigation,* **6,** 27–33.

Le Pecq, J. B., and Paoletti, C. (1966). A new fluorometric method for RNA and DNA determination. *Analytical Biochemistry,* **17,** 100–107.

Lowry, O. H., Roberts, N. R., and Kapphahn, J. H. (1957). The fluorometric measurement of pyridine nucleotides. *Journal of Biological Chemistry,* **224,** 1047–1064.

Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951). Protein measurement with the folin phenol reagent. *Journal of Biological Chemistry,* **193,** 265–275.

Maron, B. J., Ferrans, V. J., and Roberts, W. C. (1975). Ultrastructural features of degenerated cardiac muscle cells in patients with cardiac hypertrophy. *American Journal of Pathology,* **79,** 387–413.

Olsen, E. G. J. (1974). Diagnostic value of the endomyocardial bioptome. *Lancet,* **1,** 658–660.

Olsen, E. G. J. (1975). Pathological recognition of cardiomyopathy. *Postgraduate Medical Journal,* **51,** 277–281.

Parsons, D. F., Williams, G. R., and Chance, B. (1966). Characteristics of isolated and purified preparations of the outer and inner membranes of mitochondria. *Annals of the New York Academy of Sciences,* **137,** 643–666.

Peters, T. J., and de Duve, C. (1974). Lysosomes of the arterial wall. II. Subcellular fractionation of aortic cells from rabbits with experimental atheroma. *Experimental and Molecular Pathology,* **20,** 228–256.

Peters, T. J., Heath, J. R., Wansbrough-Jones, M. H., and Doe, W. F. (1975). Enzyme activities and properties of lysosomes and brush borders in jejunal biopsies from control subjects and patients with coeliac disease. *Clinical Science and Molecular Medicine,* **48,** 259–267.

Peters, T. J., Müller, M., and de Duve, C. (1972). Lysosomes of the arterial wall. I. Isolation and subcellular fractionation of cells from normal rabbit aorta. *Journal of Experimental Medicine,* **136,** 1117–1139.

Peters, T. J., and Seymour, C. A. (1976). Acid hydrolase activities and lysosomal integrity in liver biopsies from patients with iron overload. *Clinical Science and Molecular Medicine,* **50,** 75–78.

Peters, T. J., Wells, G., Brooksby, I. A. B., Jenkins, B. S., Webb-Peploe, M. M., and Coltart, D. J. (1976). Enzymic analysis of cardiac biopsy material from patients with valvular heart disease. *Lancet,* **1,** 269–270.

Reeves, W. J., and Fimognari, G. M. (1966). L lactic dehydrogenase: heart (H_4). *Methods in Enzymology,* **9,** 288–294.

Roth, J. S., Losty, T., and Wierbicki, E. (1971). Assay of proteolytic enzyme activity using a ^{14}C-labeled hemoglobin. *Analytical Biochemistry,* **42,** 214–221.

Schnaitman, C., and Greenawalt, J. W. (1968). Enzymatic properties of the inner and outer membranes of rat liver mitochondria. *Journal of Cell Biology,* **38,** 158–175.

Schwartz, A., Sordahl, L. A., Entman, M. L., Allen, J. C., Reddy, Y. S., Goldstein, M. A., Luchi, R. J., and Wyborny, L. E. (1973). Abnormal biochemistry in myocardial failure. *American Journal of Cardiology,* **32,** 407–422.

Segal, A. W., and Peters, T. J. (1976). Characterisation of the enzyme defect in chronic granulomatous disease. *Lancet,* **1,** 1363–1365.

Sekiguchi, M. (1974). Electron microscopical observations of the myocardium in patients with idiopathic cardiomyopathy using endomyocardial biopsy. *Journal of Molecular and Cellular Cardiology*, **6,** 111–122.

Seymour, C. A., and Peters, T. J. (1977). Enzyme activities in human liver biopsies: assay methods and activities of some lysosomal and membrane-bound enzymes in control tissue and serum. *Clinical Science and Molecular Medicine*, **52,** 229–239.

Sordahl, L. A., Crow, C. A., Kraft, G. H., and Schwartz, A. (1972). Some ultrastructural and biochemical aspects of heart mitochondria associated with development: fetal and cardiomyopathic tissue. *Journal of Molecular and Cellular Cardiology*, **4,** 1–10.

Thyrum, P. T., Kritcher, E. M., Luchi, R. J., and Goodkind, M. J. (1971). Effect of induced hyperthyroidism on contractile performance and cardiac myosin in the guinea pig. In *Cardiac Hypertrophy*, p. 65. Ed. by N. R. Alpert. Academic Press, New York.

Van Noorden, S., Olsen, E. G. J., and Pearse, A. G. E. (1971). Hypertrophic obstructive cardiomyopathy: a histological, histochemical and ultrastructural study of biopsy material. *Cardiovascular Research*, **5,** 118–131.

Welman, E., and Peters, T. J. (1976). Properties of lysosomes in guinea pig heart: subcellular distribution and *in vitro* stability. *Journal of Molecular and Cellular Cardiology*, **8,** 443–464.

Welman, E., and Peters, T. J. (1977). Enhanced lysosome fragility in the anoxic perfused guinea pig heart: effects of glucose and mannitol. *Journal of Molecular and Cellular Cardiology*, **9,** 101–120.

Williamson, J. R. (1966). Glycolytic control mechanisms II Kinetics of intermediate changes during the aerobic-anoxic transition in perfused rat heart. *Journal of Biological Chemistry*, **241,** 5026–5036.

Wurtman, R. J., and Axelrod, J. (1963). A sensitive and specific assay for the estimation of monoamine oxidase. *Biochemical Pharmacology*, **12,** 1439–1440.

Yang, W. C. (1963). Anaerobic functional activity of isolated rabbit atria. *American Journal of Physiology*, **205,** 781–784.

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Electrocardiographic changes during chest pain in unstable angina

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Twelve-lead electrocardiograms were recorded during one or more episodes of spontaneous chest pain in 41 patients with unstable angina. Selective coronary angiography and left ventriculography were subsequently carried out in 40 patients. In the remaining patient, the coronary arteries were examined at necropsy. Among the 29 patients with significant coronary artery disease, electrocardiographic abnormalities occurred during chest pain in 24 (83%). In 5 patients, the electrocardiogram remained unchanged during pain. It was notable that 2 of the 12 patients without significant coronary artery disease also developed electrocardiographic abnormalities during chest pain. Of the 24 patients with coronary artery disease in whom electrocardiographic abnormalities were noted, ST segment elevation and ST segment depression occurred with equal frequency (11 patients each), whereas isolated T wave abnormality was noted less frequently (2 patients). No significant differences were observed in the severity or the extent of coronary artery disease in these 3 groups of patients, though ST segment elevation appeared to be more common in patients with old myocardial infarction. Though electrocardiographic changes occur in a high proportion of patients with coronary artery disease, the diagnostic value of the electrocardiogram recorded during chest pain is limited since false positives and false negatives are encountered in a substantial proportion of patients with the clinical features of unstable angina.

The widespread application of bypass graft surgery in the treatment of coronary artery disease has led to an increased interest in the clinical evaluation of patients with unstable angina. Despite a number of studies describing correlations between clinical findings and coronary anatomy, clinical and other non-invasive techniques have been shown to be poor predictors of the presence and severity of coronary artery obstruction (Friesinger and Smith, 1972). Thus, clinical and electrocardiographic findings may suggest coronary artery disease in patients with normal coronary arteries (Likoff *et al.*, 1967; Scanlon *et al.*, 1973). They may also fail to provide any clue as to the presence of critical obstruction of the left main coronary artery (DeMots *et al.*, 1975). Though coronary angiography is the most specific means of evaluating coronary artery disease, the procedure is not entirely without risk. Further, the need to undertake urgent angiographic studies in a large number of patients often results in excessive demands on available facilities and personnel. A simple technique that would permit the selection of patients for angiography and possible surgery would, therefore, be valuable. Since the principal manifestation of unstable angina is chest pain resulting from myocardial ischaemia, it is reasonable to expect that the electrocardiogram recorded during an episode of chest pain might be useful in detecting the presence, the severity, and the location of ischaemia. The study reported herein was undertaken to test the usefulness of the electrocardiogram recorded during chest pain in identifying patients at high risk.

Patients and methods

Patients admitted with a diagnosis of unstable angina who subsequently underwent coronary angiography form the material for this study. The diagnosis of unstable angina was based on the following criteria: (1) initial onset of progressive, crescendo angina in a patient previously free from such symptoms; (2) increase in the frequency, severity, and the duration of angina in a patient with known stable angina; (3) episodes of prolonged pain not related to precipitating factors such as

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anaemia or arrhythmia; and (4) persistence of angina in spite of treatment with bed rest, nitroglycerin, and propranolol.

All patients were admitted to the cardiac unit where nurses and technicians trained to record 12-lead electrocardiograms were available. At the time of admission, each patient was instructed to report episodes of praecordial pain to the nurse. Twelve-lead electrocardiograms were recorded during, or within 1 to 2 minutes of praecordial pain, before the administration of nitroglycerin or other medication. Where recurrent episodes of pain occurred, an attempt was made to record the electrocardiogram during each episode. Patients were excluded in whom serial electrocardiographic and enzyme abnormalities compatible with acute myocardial infarction occurred. Similarly, patients with severe congestive failure were also excluded.

The electrocardiogram recorded during pain was compared with a routine resting tracing recorded on the same day and analysed for changes in the rhythm, the PR interval, the QRS axis and duration, and deviations of the ST segment and T waves. ST segment depression or elevation was considered present if there were downward or upward deviations of the ST segment of 1 mm or more. In patients with ST segment abnormality in the control tracing, a further increase in the ST segment deviation during pain was considered significant. In analysing the T waves, flattening or minor terminal inversion were disregarded. However, deep inversion, or a reversal of the polarity of the T waves was interpreted as a significant change. When ST elevation and depression occurred in the same tracing in opposite leads, ST elevation was considered the primary change and recorded as such (Fig. 1 and 2).

Selective coronary angiography was performed using the Sones or the Judkins technique. A left ventriculogram in the right anterior oblique projection was also performed in each patient. In one patient who died while awaiting angiographic studies, necropsy findings were used in correlating the electrocardiograms with the coronary anatomy. Angiograms and ventriculograms were independently examined by two groups of observers. Significant coronary artery disease was thought to be present when there was a 75 per cent or greater reduction in the estimated cross-sectional area of one or more arteries. In the case of the left main coronary artery, a 50 per cent reduction in the cross-sectional area was considered significant. These criteria were based in part on the experimental work of May *et al.* (1963). In each patient, the number of coronary arteries involved, the severity of narrowing, and the presence of collateral vessels were recorded. Left ventriculograms were reviewed for the presence and location of areas of contraction abnormality.

Results

Clinical, electrocardiographic, and angiographic data were available in 41 patients. There were 17 men and 24 women, with ages ranging between 35 and 75 years. In 13 patients, there was evidence of a previous myocardial infarction. Twelve patients were receiving digitalis at the time of the study, but none showed evidence of toxicity; ST segment and T wave abnormalities characteristic of digitalis were noted in 1 patient. In 20 patients, 2 or more electrocardiograms were recorded during successive episodes of chest pain.

Of the 41 patients, 29 had angiographic evidence

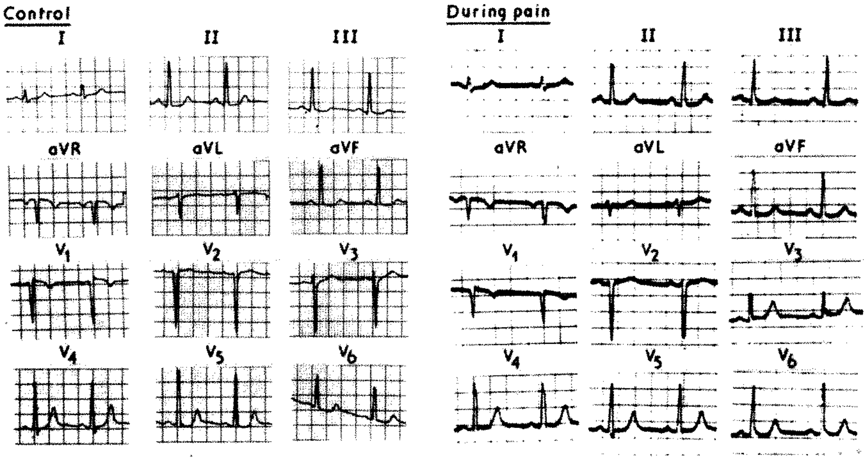

Fig. 1
Electrocardiogram recorded at rest (control), and during chest pain in a patient with normal coronary arteries. No significant ST segment and T abnormalities are noted during chest pain.

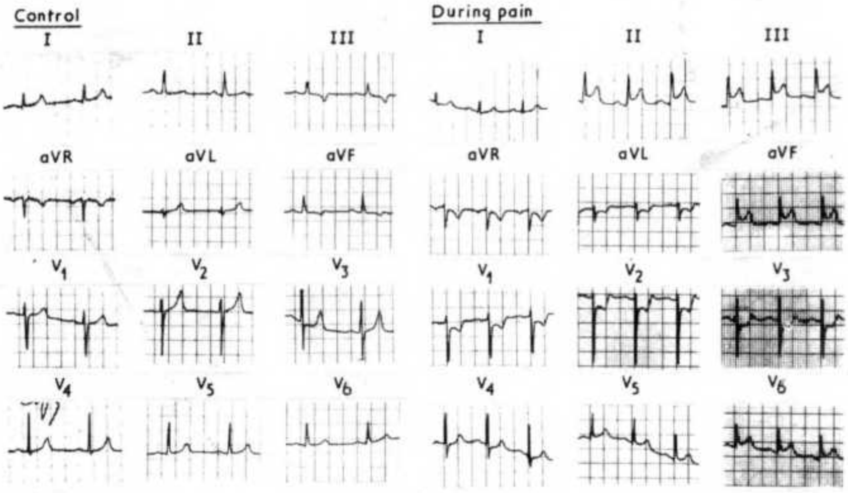

Fig. 2
Electrocardiograms recorded at rest and during chest pain in a patient with significant disease involving the right and left anterior descending coronary arteries (see Fig. 3). During pain, there is a reversal of T wave polarity in leads III and aVF and significant ST segment elevation in leads II, III, aVF, and V6. ST segment depression is present in leads aVL and V1 to V3.

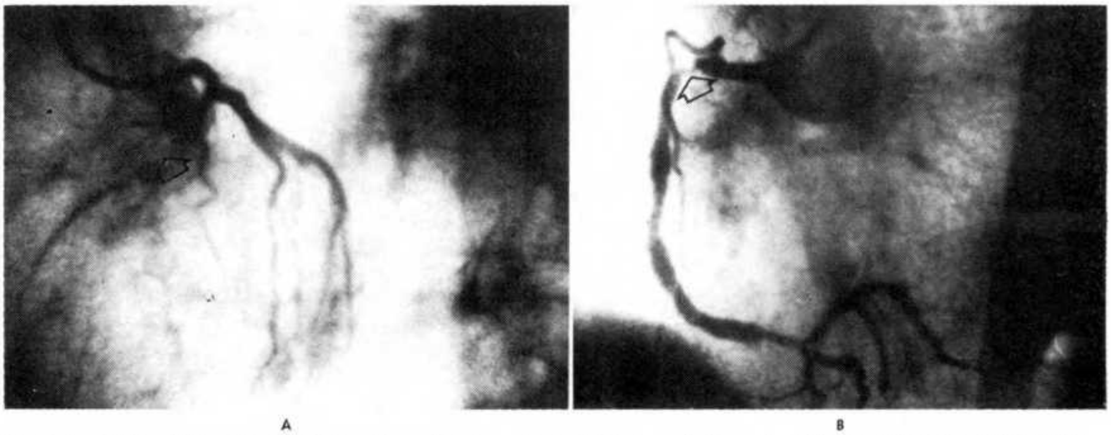

Fig. 3 A and B *Representative frames from the coronary arteriograms of the patient illustrated in Fig. 2. Note the segmental occlusion (arrow, A) in the proximal part of the left anterior descending coronary artery. The right coronary arteriogram (B) shows discrete subtotal occlusion proximally (arrow), and diffuse disease along its entire length.*

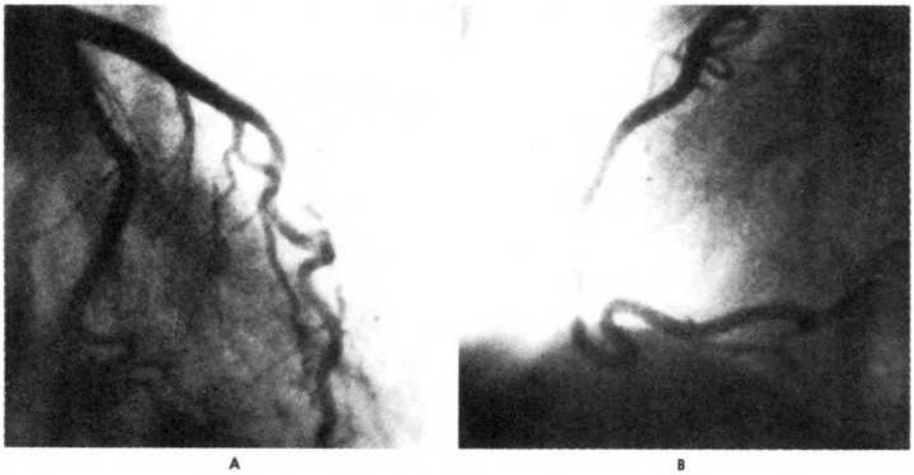

Fig. 4 A and B
Coronary arteriograms of the patient illustrated in Fig. 1. Both the left (A), and the right (B) coronary arteries are free from disease.

of significant coronary artery disease (Fig. 3). Among the 12 patients without significant coronary artery disease as defined above, there were 9 patients in whom the coronary arteries were entirely normal (Fig. 4). In the remaining 3, there were luminal irregularities, or 30 to 50 per cent reduction in the estimated cross-sectional area of one or more of the coronary arteries. Details of the angiographic findings together with the other data are shown in Table 1.

With the exception of one patient in whom slight widening of the QRS complexes occurred in conjunction with ST-T abnormality during chest pain, the electrocardiographic changes during pain were confined to the ST segments and the T waves. Of the 29 patients with significant coronary artery disease, 24 developed electrocardiographic abnormalities during episodes of chest pain. In 5 of these patients, these changes occurred in the face of a normal resting electrocardiogram, whereas in 19, they were superimposed on an abnormal resting tracing. In 3 patients, the first electrocardiogram during pain indicated no significant change. However, subsequent tracings during chest pain disclosed ST segment and T wave abnormality. Except for these 3 patients, the type of ST segment and T wave abnormality noted during pain was similar in each patient, though there was some variability in the degree of abnormality during different episodes of pain. Of the 5 patients with coronary artery disease in whom the electrocardiogram was unchanged during pain, the disease involved a single vessel in 2, two vessels in 1, and three vessels in the remaining 2 patients (see Table 1). Among the 12 patients without significant coronary artery disease, the resting electrocardiogram was normal in 5, and showed ST segment and T abnormality in 7. In 10 of these 12 patients, no electrocardiographic abnormalities were observed during pain. ST segment and T wave abnormalities were noted during pain in the remaining 2 patients. The coronary arteries were entirely normal in the latter 2 patients. However, both had been taking digitalis at the time of the study.

The commonest electrocardiographic abnormality during chest pain consisted of significant deviations of the ST segment, with or without concomitant T wave abnormality. Isolated T wave abnormality was noted only in 2 patients. ST segment elevation and ST segment depression were noted with equal frequency in patients with coronary artery disease (11 patients each). ST segment elevation was usually confined to 2 or 3 adjacent leads, whereas ST segment depression tended to be diffuse, involving multiple leads. No significant differences were noted between these two groups of patients with respect to the severity of coronary narrowing, the number of vessels involved, or the presence of collateral vessels. There was also no significant difference in the incidence of left ventricular contraction abnormalities (Table 2). However, a greater proportion of patients with ST segment elevation had had previous myocardial infarctions. Further, in the patients with previous myocardial infarction in whom ST segment elevation occurred during pain, the abnormalities were seen to overlie the site of the old infarction.

There was no relation between the severity of coronary obstruction or the number of vessels involved, and the degree of electrocardiographic abnormality during pain. However, the location of the electrocardiographic abnormality during pain predicted the presence of significant disease in arteries known to be the major source of supply to the corresponding area of the myocardium. Thus, anterior (V1 to V4), lateral (I, aVL, V5, and V6), or anterior and lateral changes were associated with significant disease in the left anterior descending coronary artery. Similarly, inferior (II, III, aVF), or inferolateral (II, III, aVF, V5, V6) changes were noted in patients with disease in the right coronary or the circumflex coronary artery. Electrocardiographic abnormalities in the anterior, lateral, and inferior leads were associated with combined disease of the left anterior descending, right coronary, and the circumflex arteries.

Discussion

Although the electrocardiographic abnormalities during spontaneous angina are well known, there is little information concerning the frequency, or the diagnostic significance of such abnormalities in patients with unstable angina. In a group of 54 patients with preinfarction angina, Gazes *et al.* (1973), observed electrocardiographic changes during chest pain in 49 (90%). Coronary angiography was not performed in any of the patients in this report. The need for coronary angiographic data in correlative studies of this type is apparent from the observation that a substantial number of patients with symptoms of unstable angina are free from significant coronary artery disease (Scanlon *et al.*, 1973). In the study reported here, it was noted that electrocardiographic changes occurred in a proportion of patients (83%) similar to that reported by Gazes *et al.* (1973). On the other hand, similar electrocardiographic abnormalities were noted in 2 of the 12 patients without coronary artery disease. Since the inclusion of patients with 30 to 50 per cent obstruction in the

Table 1 *Electrocardiographic and angiographic data*

Case No.	*Age (y)*	*Sex*	*Electrocardiogram*		*Coronary lesions*	*Ventriculogram*
			Control	*During pain*		
1	56	F	Old post. infarct. T ↓ II, III, F	ST ↑ II, III, F	RCA LAD CX	Diffuse hypokinesia
2	45	M	Old inf. infarct. ST and T ↓ II, III, F	ST ↓ I, V5, V6	RCA Marginal	Hypokinesia, inf. wall and apex
3	48	F	Old subendo. infarct. T ↓ I, L, V1 to V3	No change	LAD	Normal
4	52	F	Old ant. sep. infarct. T ↑ ↓ V1 to V3	No change	LAD RCA	Dyskinesia, apex
5	35	M	Normal	ST ↑ V1 to V4	LAD	Normal
6	65	M	Old ant. sep. infarct. ST and T ↓ II, III, F, V5, V6	ST ↑ V4 to V6	LAD Marginal	Hypokinesia, ant. wall
7	47	M	T ↓ II, III, F	ST ↑ II, III, F, V5, V6	RCA LAD	Normal
8	52	F	T ↓ V1 to V3	No change	None	Normal
9	63	F	Old ant. sep. infarct. T ↓ V1 to V3	ST ↑ V1 to V3 T ↑ V1 to V3	RCA (graft) LAD (graft)	Diffuse hypokinesia
10	52	F	Minimal ST ↓ I, L, V4 to V6	ST ↓ I, L, V4 to V6	RCA LAD	Diffuse hypokinesia
11	60	M	T ↓ I, L, V1, V2	ST ↑ V1 to V4	LAD	Normal
12	55	M	Old inf. post. infarct. T ↑ ↓ I, L, V1 to V6	ST ↓ I, L, V1 to V6	Left main	Hypokinesia, anterior wall
13	54	M	ST ↓ V4 to V6	ST ↓ II, III, F, V3 to V6	RCA LAD CX	Dyskinesia, apex
14	42	F	Normal	ST ↑ L	RCA LAD	Normal
15	57	M	T ↓ II, III, F	ST ↓ V3 to V6 T ↓ I, L, V1 to V6	LAD CX	Hypokinesia, anterial wall
16	62	M	Normal	No change	CX	Normal
17	62	F	Old subendo. infarct. T ↓ II, III, F, V3 to V6	ST ↑ II, III, F	RCA CX	Normal
18	53	F	Normal	ST ↓ V2 to V6 T ↓ V1 to V6	RCA LAD	Normal
19	52	M	Normal	ST ↓ I, L, V1 to V6 T ↓ I, L, V1 to V6	LAD CX	None*
20	50	F	T ↑ ↓ V1 to V3	T ↓ I, L, V1 to V4	RCA CX LAD	Hypokinesia, anterior wall
21	58	M	Old inf. infarct. T ↓ II, III, F	ST ↑ III, F T ↑ II, III, F	RCA LAD CX	Dyskinesia, inferior wall
22	75	F	Old inf. infarct. T ↓ I, L, V4 to V6	ST ↓ I, L, V4 to V6	RCA CX LAD	Dyskinesia, inferior wall and apex
23	65	M	Normal	ST ↓ V4 to V6 T ↓ II, III, F	RCA CX LAD	Normal
24	49	F	Normal	No change	RCA LAD CX	Normal
25	33	M	Normal	No change	None	Normal
26	43	F	T ↑ ↓ II, III, F	No change	None	Normal
27	42	M	Diffuse ST sagging	No change	None	Normal
28	56	M	Old ant. infarct. ST ↓ II, III, F	ST ↑ V2 to V4	RCA CX LAD	Aneurysm, apex
29	63	F	T ↓ V2 to V6	No change	None	Normal
30	48	F	Normal	No change	None	Normal
31	35	F	T ↓ II, III, F, V5, V6	No change	None	Normal
32	42	F	T ↓ II, III, F	No change	None	Normal
33	51	M	Old inf. infarct. T ↓ I, L, V3 to V6	ST ↑ V2 to V5	RCA LAD CX	Aneurysm, anterior wall
34	63	F	T ↓ II, III, F, V4 to V6	T ↑ II, III, F	RCA	Hypokinesia, inferior wall
35	72	F	ST ↓ V4 to V6, T ↓ V4 to V6	No change	None	Normal
36	58	F	ST ↓ I, II, L, V4 to V6	ST ↓ I, II, L, V2 to V6	None	Normal
37	64	F	T ↓ II, III, F, V4 to V6	ST ↓ I, II, V2 to V6	RCA	Normal
38	54	M	T ↓ II, III, F, V4 to V6	ST ↓ I, II, L, V2 to V6	Left main RCA CX	Normal

Table 1 *Continued*

Case No.	*Age (y)*	*Sex*	*Electrocardiogram*		*Caronary lesions*	*Ventriculogram*
			Control	*During pain*		
39	61	F	Old inf. lat. and ant. infarcts. ST ↓ V4 to V6 T ↓ II, III, F, V4 to V6	No change	LAD RCA CX	Diffuse hypokinesia
40	57	F	T ↑ ↓ I, L, V4 to V6	No change	None	Normal
41	69	F	ST ↓ V3 to V6 T ↑ ↓ V3 to V6	ST ↓ V2 to V4 T ↓ V2 to V4	None	Normal

Abbreviations: RCA = Right coronary artery
LAD = Left anterior descending
CX = Circumflex

Symbols: ↑ = elevation
↓ = depression, inversion
↑ ↓ = diphasic
*Necropsy.

Table 2 *Relation of ST segment abnormality to angiographic findings**

Electrocardiogram	*No. of vessels involved*					*Abnormal ventriculogram*	*Collateral vessels*	*Old infarction*
	None	*Single*	*Double*	*Triple*	*L. main*			
ST elevation	0	1	5	5	0	6	5	6
ST depression	2	1	5	3	2	6	6	3
No ST deviation	10	2	1	2	0	2	1	3

*In 39 patients (excluding 2 with isolated T wave abnormality).

group without coronary artery disease may be considered arbitrary, it should be emphasised that the coronary arteries were entirely normal in the 2 patients in whom electrocardiographic changes were noted during pain. The absence of electrocardiographic abnormalities during pain in 5 patients with coronary artery disease, and their development in 2 patients with normal coronary arteries suggests that the value of electrocardiography during pain in separating patients with coronary artery disease from those without is severely limited. The reasons underlying the absence of electrocardiographic abnormalities in the 5 patients with coronary artery disease are unclear. One might speculate that ischaemia might not have been sufficiently severe or prolonged to give rise to electrocardiographic abnormality, or that ischaemia may have occurred in areas of the myocardium that are electrically silent. A similar uncertainty exists regarding the development of electrocardiographic abnormality during chest pain in the 2 patients with normal coronary arteries. Such changes during exercise have in the past been attributed to digitalis therapy, or vasoregulatory abnormalities (Friesinger *et al.*, 1972). The spontaneous occurrence of coronary artery spasm has been well documented (Chahine and Luchi, 1976) and is an additional possibility to be considered. Though spasm was not shown during angiography in any of the patients in this study, the possibility that it might have occurred at other times cannot be entirely ruled out since it has been suggested that the tendency to develop spasm may be masked by the routine administration of vasodilators during coronary angiography (Chahine *et al.*, 1975).

Neither the degree of ST segment and T wave abnormality, nor its extent seemed to have any relation to the severity of coronary artery disease. However, a relation was noted between the location of the electrocardiographic abnormalities and the site of the disease in the coronary arteries. Thus, electrocardiographic abnormalities in the anterior and the lateral leads were associated with disease in the left anterior descending and the marginal arteries. Similarly, changes in the inferior and the inferolateral leads occurred in patients with right coronary and circumflex disease. Though ST segment and T wave changes were indicative of disease in the arteries supplying corresponding areas of the myocardium, significant additional disease involving other vessels was also noted. This was particularly common in the case of the right coronary artery (Table 1). Whether this was the result of a relative insensitivity of the electrocardiographic leads to the occurrence of ischaemia in the inferior wall could not be determined.

Since its recognition as a cardinal feature of the variant form of angina pectoris, there has been considerable interest in the occurrence of ST segment elevation during angina. Early clinical studies (Prinzmetal *et al.*, 1959) suggested that this phenomenon was the result of severe ischaemia resulting from critical stenosis of a large coronary artery. It has subsequently been shown that ST segment elevation during chest pain may occur in association with a variety of arteriographic patterns (Silverman and Flamm, 1971; MacAlpin *et al.*, 1973; Oliva *et al.*, 1973). Plotnick and Conti (1975), in a recent study, concluded that ST segment elevation during pain had no predictive value with respect to the angiographic anatomy, or left ventricular dynamics. The results in this present study confirm and extend the observations made by Plotnick and Conti. Thus, ST segment elevation was observed frequently in patients with unstable angina. Further, there were no significant differences between patients with the two types of ST segment abnormality during chest pain with respect to the severity of coronary disease, or the presence of left ventricular contraction abnormalities. In contrast to the findings of Plotnick and Conti, however, there was a preponderance of patients with old myocardial infarction in the group showing ST segment elevation. It is notable that a similar ST segment elevation has been observed in leads overlying an old myocardial infarction during exercise tests (Kattus, 1974). Experimental studies by Ekmekci *et al.* (1961) have suggested that in comparison with ST segment depression, ST segment elevation signifies more severe ischaemia. Whether the presence of an old myocardial infarction predisposes to, or simply reflects more severe ischaemia in patients with ST segment elevation as observed in this study is not clear.

References

Chahine, R. A., and Luchi, R. J. (1976). Coronary arterial spasm: culprit or bystander? *American Journal of Cardiology*, **37**, 936–937.

Chahine, R. A., Raizner, A. E., Ishimori, T., Luchi, R. J., and McIntosh, H. D. (1975). The incidence and clinical implications of coronary artery spasm. *Circulation*, **52**, 972–978.

DeMots, H., Bonchek, L. I., Rösch, J., Anderson, R. P., Starr, A., and Rahimtoola, S. H. (1975). Left main coronary artery disease. Risks of angiography, importance of co-existing disease of other coronary arteries, and effects of revascularization. *American Journal of Cardiology*, **36**, 136–141.

Ekmekci, A., Toyoshima, H., Kwoczynski, J. K., Nagaya, T., and Prinzmetal, M. (1961). Angina pectoris. IV. Clinical and experimental difference between ischemia with ST elevation and ischemia with ST depression. *American Journal of Cardiology*, **7**, 412–426.

Friesinger, G., Biern, R. O., Likar, I., and Mason, R. E. (1972). Exercise electrocardiography and vasoregulatory abnormalities. *American Journal of Cardiology*, **30**, 733–740.

Friesinger, G., and Smith, R. (1972). Correlation of electrocardiographic studies and arteriographic findings with angina pectoris. *Circulation*, **46**, 1173–1184.

Gazes, P. C., Mobley, E. M., Faris, H. M., Duncan, R.C., and Humphries, G. B. (1973). Pre-infarctional (unstable) angina—a prospective study—ten-year follow-up. Prognostic significance of electrocardiographic changes. *Circulation*, **48**, 331–337.

Kattus, A. A. (1974). Exercise electrocardiography: recognition of the ischemic response, false positive and false negative patterns. *American Journal of Cardiology*, **33**, 721–731.

Likoff, W., Segal, B., and Kasparian, H. (1967). Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. *New England Journal of Medicine*, **276**, 1063–1066.

MacAlpin, R. N., Kattus, A. A., and Alvaro, A. B. (1973). Angina pectoris at rest with preservation of exercise capacity. Prinzmetal's variant angina. *Circulation*, **47**, 946–958.

May, A. G., DeWeese, J. A., and Rob, C. G. (1963). Hemodynamic effects of arterial stenosis. *Surgery*, **53**, 513–524.

Oliva, P. B., Potts, D. E., and Pluss, R. G. (1973). Coronary artery spasm in Prinzmetal angina. Documentation by coronary arteriography. *New England Journal of Medicine*, **288**, 745–751.

Plotnick, G. D., and Conti, C. R. (1975). Transient ST segment elevation in unstable angina. Clinical and hemodynamic significance. *Circulation*, **51**, 1015–1019.

Prinzmetal, M., Kennamer, R., Merliss, R., Wada, T., and Bor, N. (1959). Angina pectoris. I. A variant form of angina pectoris. *American Journal of Medicine*, **27**, 375–388.

Scanlon, P. J., Nemickas, R., Moran, J. F., Talano, J. V., Amirparviz, F., and Pifarre, R. (1973). Accelerated angina pectoris. Clinical, hemodynamic, arteriographic, and therapeutic experience in 85 patients. *Circulation*, **47**, 19–26.

Silverman, M. E., and Flamm, M. D. (1971). Variant angina pectoris. Anatomic findings and prognostic implications. *Annals of Internal Medicine*, **75**, 339–343.

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Determinants of angina in aortic stenosis and the importance of coronary arteriography

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Coronary arteriography was performed in 140 patients with aortic stenosis (peak systolic gradient > 50 mmHg). Coronary artery disease was found in 32 patients (23%) of whom 9 (6%) had no history of angina. Fifty-six patients (40%) presented with angina but had normal coronary arteriograms. Effort syncope was a presenting symptom in 34 patients of whom 9 had coronary artery disease.

Patients with angina but normal coronary arteriograms had significantly greater peak left ventricular pressures, peak systolic gradients, left ventricular end-diastolic pressures, and left ventricular masses than angina-free patients with normal coronary arteriograms. The ratio of diastolic pressure-time index (DPTI) to tension time index (TTI) and the aortic valve area were less in the patients with angina and normal coronary arteries than in angina-free patients. These findings support the concept of oxygen demand exceeding supply in patients with severe aortic stenosis and normal coronary arteries.

Two surgical problems were related to operative mortality: a long bypass time and difficulty with coronary artery perfusion. High quality selective coronary arteriograms are essential in all patients undergoing cardiac catheterisation for aortic stenosis if anatomical problems with coronary artery perfusion are to be avoided.

Angina pectoris has long been recognised as a presenting symptom of aortic stenosis (Contratto and Levine, 1937; Lewes, 1951; Mitchell *et al.*, 1954; Wood, 1958; Braunwald *et al.*, 1963), often in the presence of normal coronary arteries (Levine, 1951; Linhart *et al.*, 1968). Angina in this situation is clinically indistinguishable from that caused by occlusive coronary artery disease (Wood, 1968).

Many patients with severe aortic stenosis may have additional coronary artery disease (Basta *et al.*, 1975; Mandal and Gray, 1976), and this is known to be a major factor in left ventricular function after aortic valve replacement (Linhart and Wheat, 1967). Saphenous vein bypass grafting is now possible with aortic valve replacement (Loop *et al.*, 1972; Merin *et al.*, 1973). Preliminary results vary, some groups reporting a higher earlier mortality (Berndt *et al.*, 1974; Callard *et al.*, 1976), and others a reduced mortality (Moraski *et al.*, 1976).

Coronary arteriography carries a small but definite morbidity and mortality (Emanuel, 1975), and several workers have attempted to delineate which patients with aortic stenosis should have coronary arteriography at cardiac catheterisation. Bonchek *et al.* (1973) suggest it may be omitted in patients with no symptoms of ischaemic heart disease, while Mandal and Gray (1976) suggest it may be omitted in patients under 40. Nevertheless it is recognised that patients without angina may have coronary artery disease (Harris *et al.*, 1975).

This study presents our findings at cardiac catheterisation in 140 patients with aortic stenosis, all of whom had selective coronary arteriography at cardiac catheterisation.

The surgical results are presented of 122 patients, both elective and emergency, who proceeded to aortic valve surgery in this hospital, between 1971 and 1976. Factors involved in the operative mortality are discussed.

Patients and methods

Studies were made on 140 patients aged 18 to 75 (mean age 60) with full informed consent; 50 of these patients were women.

The most common presenting symptom was exertional dyspnoea in 116 patients; 79 patients

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had angina. Effort syncope had occurred in 34 patients and 9 presented with systemic emboli. Three patients were asymptomatic.

Patients were premedicated with atropine 0·6 mg and diazepam 10 mg intramuscularly. Pressures were measured by Statham P23 Gb transducers using the sternal angle as a reference point, and were recorded on a Cambridge 12-channel instrument. Aortic valve area was calculated using the method of Gorlin and Gorlin (1951) from simultaneous recordings of aortic and left ventricular pressure. In these studies the left ventricular pressure was obtained from a catheter advanced via a 'teflon' sheath across the atrial septum and down through the mitral valve (Brooksby *et al.*, 1974). This technique of transseptal puncture avoids haemodynamic changes produced by a catheter through a narrow orifice, and the risk of producing systemic emboli by knocking plaques of calcium off the aortic valve.

Cardiac output was measured by indocyanine green-dye dilution from duplicate curves using a Gilford densitometer.

In patients with mild aortic regurgitation the cardiac output used for the calculation of aortic valve area was derived from angiographic volume analysis. Patients with more than mild aortic regurgitation were excluded from calculations of valve area. Left ventricular volumes were calculated using the single plane area-length method and a light pen-computer system. Left ventricular mass was calculated using the method of Kennedy *et al.* (1970).

The diastolic pressure-time index (DPTI) and the tension time index (TTI) were derived from simultaneous aortic and left ventricular pressure recordings using the methods of Sarboff *et al.* (1958 and Buckberg *et al.* (1975). The ratio of DPTI:TTI is thus calculated as:

$$\frac{\text{Mean (Ao-LV) pressure in diastole} \times \text{diastolic filling time} \times \text{heart rate}}{\text{Mean LV pressure in systole} \times \text{LV ejection time} \times \text{heart rate}}$$

and represents myocardial oxygen supply : myocardial oxygen demand.

Selective coronary arteriography was performed using the Judkins technique in 128 patients and the Sones technique in 12.

Aortic stenosis was defined as a peak systolic gradient >50 mmHg or a calculated aortic valve area of <0·5 cm².

Only left ventriculograms and pressure recordings of high quality were used for analysis, and 10 successive cycles were used for calculations of valve area and DPTI:TTI.

Results were statistically analysed using Student's unpaired t test.

Results

(1) CARDIAC CATHETER RESULTS

Of the 140 patients studied, 79 had angina (Table 1). Of these, 56 had normal coronary arteriograms. Sixty-one patients had no history of angina and of these 9 had abnormal coronary arteriograms. The youngest patient with coronary artery disease was aged 38.

Table 2 shows the results in the patients with normal coronary arteriograms divided into those with a history of angina and those who were free of angina. There was a significantly greater peak left ventricular pressure, peak systolic gradient, and left ventricular end-diastolic pressure in those patients with angina. The left ventricular end-diastolic volume index was similar in the two groups. Patients with angina had smaller aortic valve areas, a smaller DPTI/TTI ratio, and a greater left ventricular mass than patients without angina.

Table 3 shows the results in the patients with angina divided into normal and abnormal coronary artery groups. In this study the only significant differences were that patients with abnormal coronary arteries had a lower peak left ventricular pressure and a lower peak systolic gradient across the aortic valve. Other variables were similar in the two groups.

Table 4 shows the results in the 25 patients who had experienced syncope compared with 83 patients who had not had this symptom (all patients with normal coronary arteriograms). Patients with a history of syncope on effort had higher resting peak systolic gradients and higher peak left ventricular pressures than the non-syncopal group. In those patients in whom good left ventriculograms were obtained, the left ventricular end-diastolic volume index was found to be smaller in the syncopal group.

(2) SURGICAL RESULTS

One hundred and twenty-two patients proceeded to aortic valve surgery at this hospital. The mean time from cardiac catheterisation to operation was 40 days. One hundred and one patients received Starr-Edwards prostheses, 19 had Bjork-Shiley prostheses, 1 patient had an aortic homograft, and 1 patient had an aortic valve decalcification. Two patients had a triple valve replacement, 8 had aortic and mitral valve replacements, 2 had aortic valve replacement plus open mitral valvotomy, and 6 patients had an aortic valve replacement plus one or more saphenous vein bypass grafts. There were 14 deaths (hospital mortality 11%).

Table 5 shows two main factors that were found to be important during operation in the 14 patients who died: coronary artery perfusion problems and a long bypass time. Coronary artery perfusion problems were pre-existing coronary artery disease (in 3), local anatomical problems such as double left coronary ostia (in 2), small right coronary ostia (in 3), or very heavy valve calcification involving the coronary ostia (in 2). A long bypass time occurred in those patients requiring additional mitral valve surgery. One of these also had a small right coronary ostium. Of the 6 patients requiring saphenous vein bypass grafting, 1 died.

Of the remainder 3 patients refused operation and 2 died within 19 months of cardiac catheterisation. Four patients died suddenly before aortic valve replacement could be performed. Two of these patients had severe coronary artery disease in addition to aortic stenosis, and the other 2 had a peak systolic gradient >95 mmHg. Six patients were considered unsuitable for heart operation; 3 of these had widespread coronary artery disease and poor left ventricular function, 1 had severe renal disease, 1 had grossly impaired lung function, and 1 had generalised arteriosclerosis. Three of these patients considered inoperable have died. Three patients are on the urgent surgical waiting list. Two patients were operated on elsewhere.

Discussion

Angina is a common symptom in patients with severe aortic valve stenosis who have normal coronary arteries proven by selective arteriography (Basta *et al.*, 1975; Mandal and Gray, 1976). The demonstration of lactate production or decreased lactate uptake in such patients under haemodynamic stress suggests that myocardial oxygen consumption exceeds the available supply (Fallen *et al.*, 1967).

Three factors predominantly determine myocardial oxygen consumption: heart rate (Laurent *et al.*, 1955), velocity of contraction (Sonnenblick

Table 1 *Incidence of angina syncope and coronary artery disease in 140 patients*

	Normal coronary arteriograms	*Abnormal coronary arteriograms*
Angina	56 (40%)	23 (16%)
No angina	52 (37%)	9 (6%)
Syncope	25 (18%)	9 (6%)

Table 2 *Aortic stenosis and normal coronary arteriograms*

	Angina	*No angina*	*Significance*
	n=49	n=42	
Peak LVP (mmHg)	209 ±26	191 ±32	P=0·003
Peak systolic gradient (mmHg)	94 ±25	79 ±26	P=0·007
LVEDP (mmHg)	15 ±9	10 ±7	P=0·005
LVEDVI (ml/m²)	92 ±39	98 ±43	NS
	n=26	n=24	
Aortic valve area (cm²)	0·51 ±0·16	0·62 ±0·17	P<0·008
DPTI/TTI	0·49 ±0·18	0·62 ±0·24	P<0·04
LV mass (g)	362 ±143	266 ±82	P<0·006

LVP, left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index; DPTI, diastolic pressure-time index; TTI, tension time index. Results are expressed as mean ±1 SD.

Table 3 *Aortic stenosis and angina*

	Normal coronaries	*Abnormal coronaries*	*Significance*
	n=49	n=23	
Peak LVP (mmHg)	209 ±26	194 ±38	P<0·05
Peak systolic gradient (mmHg)	94 ±25	80 ±26	P=0·04
LVEDP (mmHg)	15 ±9	13 ±8	NS
LVEDVI (ml/m²)	92 ±39	88 ±45	NS
	n=26		
Aortic valve area (cm²)	0·49 ±0·18	0·53 ±0·17	NS
LV mass (g)	362 ±143	291 ±129	NS

LVP, left ventricular pressure; LVEDP, left ventricular end diastolic pressure; LVEDVI, left ventricular end diastolic volume index.
Results are expressed as mean ±1 SD.

Table 4 *Aortic stenosis, syncope, and normal coronary arteriograms*

	Effort syncope	*No effort syncope*	*Significance*
	n=25	n=83	
Peak systolic gradient (mmHg)	98 ±23	81 ±26	P=0·005
Peak LV pressure (mmHg)	208 ±27	194 ±32	P<0·05
LVEDP (mmHg)	11 ±7	13 ±9	NS
	n=20	n=50	
Aortic valve area (cm²)	0·52 ±0·16	0·58 ±0·17	NS
LVEDVI (ml/m²)	79 ±34	100 ±43	P<0·05

LVEDP, left ventricular end-diastolic pressure; LVEDVI, left ventricular end-diastolic volume index.
Results are expressed as mean ±1 SD.

Table 5 *Operative problems in deaths from aortic valve replacement*

	No.
Hospital deaths	14
Problems with coronary artery perfusion	
Pre-existing coronary artery disease	3
Double left coronary ostia	2
Small right coronary ostia	3
Ostial calcium extending from valve	2
Long bypass time	
Additional mitral valve surgery	5

et al., 1965), and left ventricular wall tension (Rodbard *et al.*, 1964). Exercise or emotion which most commonly precipitate angina increase all three factors. The dangers of provoking angina or syncope in patients with aortic stenosis precluded studies during exercise. Data are presented from studies at rest of two determinants of wall tension: left ventricular volume and systolic pressure. From the law of Laplace the wall stress of a chamber is related directly to the square of the radius and to the intracavity pressure, and inversely to the wall thickness (corresponding, in this instance, to the left ventricular volume, systolic pressure, and mass, respectively). In the patients studied who had angina but normal coronary arteriograms both the mean left ventricular mass and the peak systolic gradient were significantly higher and the aortic valve area significantly lower than in those without angina. The significant correlation of these three closely related variables suggests that increased wall tension is related to the occurrence of angina. It is of interest that no correlation was found with left ventricular volume.

It is likely, but by no means obvious from either this series or others (Fallen *et al.*, 1967; Buckberg *et al.*, 1975), that the aortic valve area is the critical factor. A small aortic orifice requires high left ventricular pressures to maintain flow across the valve in systole and results in inefficient conversion of pressure energy into flow energy because of losses caused by increasing turbulence of the jet (Bellhouse, 1972). The raised left ventricular pressure will lead to an increase in mass by hypertrophy.

Myocardial blood supply is also affected by aortic valve stenosis. Studies in mechanical models indicate that a decrease in aortic valve area will result in a low aortic perfusion pressure (Bellhouse and Bellhouse, 1969). The effective coronary perfusion pressure will be further reduced by the higher than normal diastolic pressure in the hypertrophied ventricle and by the increased wall thickness itself. In addition, a Venturi effect at the coronary ostia may impair or even reverse coronary flow during systole (Bellhouse and Bellhouse, 1969). The calculation of aortic valve area is subject to many pitfalls, but the correlation of decreased area and its dependent variables (peak gradient and left ventricular mass) with angina in our cases does suggest that this ominous symptom is related to the severity of the valve stenosis.

The combination of decreased coronary flow and increased left ventricular work leads to a lower oxygen supply with a higher demand. The ratio of DPTI:TTI represents this supply to demand ratio and was lower in the angina group. However, the standard deviations overlap, and we have not found it to be as specific as others in studies of ischaemia in aortic stenosis (Fallen *et al.*, 1967). Studies of Hoffman and Buckberg (1975) in dogs suggest that a ratio of 0·5 or less indicates subendocardial ischaemia. In this study of patients with normal coronary angiograms 54 per cent of 26 patients with angina had a ratio of less than 0·5, but 33 per cent of 24 patients without angina also had a ratio less than 0·5.

Effort syncope in aortic stenosis may be caused by the high ventricular pressure firing baroreceptors to produce reflex bradycardia and vasodilatation (Johnson, 1971). In this series, patients with syncope had higher peak left ventricular pressures and higher peak systolic gradients than those who did not have this symptom.

It may not be necessary to invoke baroreceptor activity. The normal vasodilatation in skeletal muscle during exercise in patients who are unable to increase their cardiac output sufficiently may be enough to cause a dramatic fall in blood pressure. This hypotension with no rhythm disturbance on exercise has been recorded clinically (Flamm *et al.*, 1967), but only in the standing position.

Patients with a history of syncope on effort and normal coronary arteriograms had smaller left ventricular end-diastolic volume indices than those without the symptom. These volumes were measured in the recumbent patient and probably represented the maximal end-diastolic volumes on upright exertion (Wang *et al.*, 1960). Because of the lower left ventricular end-diastolic volume indices in this group, the stroke volume would be smaller for any given ejection fraction. An increased ejection fraction with exertion (if it occurred at all in these patients) would also produce little increase in stroke volume. It is likely, therefore, that on exertion the cardiac output would be lower, and almost entirely rate dependent, in the group with syncope.

Coronary arteriography was performed routinely on all patients, with no mortality. The only haemodynamic variables which differed in patients with and without coronary artery disease were the peak left ventricular pressure and peak systolic gradient which were lower in patients with coronary artery disease (Table 3). This agrees with previous studies (Mandal and Gray, 1976), but could not adequately predict coronary artery disease. The absence of angina does not preclude coronary artery disease, which was present in 6 per cent of our patients without angina. Age has been suggested as a helpful guide, and that patients under 40 do not need coronary arteriography (Mandal and Gray, 1976). However, one of our patients who needed saphenous vein bypass grafting for coronary artery disease as well as aortic valve replacement was aged 38. In our experience coronary arteriography has three principal roles:

(1) To exclude patients from operation in whom the combination of severe aortic stenosis, widespread diffuse coronary artery disease, and impaired left ventricular function presents an unacceptable surgical risk. In this series 3 patients were excluded on this basis.

(2) To delineate stenotic coronary lesions which may require saphenous vein bypass grafting. In our series this was performed on 6 patients, 5 of whom survived.

(3) To define the anatomy of the coronary ostia. Analysis of the surgical problems in the 14 patients who died (Table 5) showed that in 7 patients great difficulty was experienced at intubating the coronary ostia at cardiopulmonary bypass. The ventricular mass in these patients is high and even minor defects of coronary perfusion during bypass jeopardise myocardial function. Myocardial infarction has been reported to occur in 15 to 18 per cent of patients during aortic valve replacement (Follath and Ginks, 1972; Sharratt *et al.*, 1976), and accounted for 80 per cent of the deaths in a recent series (Sharratt *et al.*, 1976).

High quality coronary arteriograms are needed to differentiate between a left coronary artery which bifurcates immediately and one which has two ostia. In the latter situation the ostia may be too small to admit perfusion cannulae, when only one may be perfused. In this series 2 out of 3 patients who had a left coronary artery with 2 ostia, died. The condition was diagnosed preoperatively in only 1. There may be considerable difficulty in perfusing the left coronary artery which bifurcates immediately (Fox *et al.*, 1973).

We consider coronary arteriography is essential in all patients before aortic valve replacement if the surgical mortality for this condition is to be reduced.

References

Basta, L. L., Raines, D., Najjar, S., and Kioschos, J. M. (1975). Clinical, haemodynamic, and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease. *British Heart Journal,* **37,** 150–157.

Bellhouse, B. J. (1972). The fluid mechanics of heart valves. In *Cardiovascular Fluid Dynamics,* pp. 261–285. Ed. by D. H. Bergel. Academic Press, London and New York.

Bellhouse, B., and Bellhouse, F. (1969). Fluid mechanics of model normal and stenosed aortic valves. *Circulation Research,* **25,** 693–704.

Berndt, T. B., Hancock, E. W., Shumway, N. E., and Harrison, D. C. (1974). Aortic valve replacement with and without coronary artery bypass surgery. *Circulation,* **50,** 967–971.

Bonchek, L. I., Anderson, R. P., and Rösch, J. (1973). Should coronary arteriography be performed routinely before valve replacement? *American Journal of Cardiology,* **31,** 462–466.

Braunwald, E., Goldblatt, A., Aygen, M. M., Rockoff, S. D., and Morrow, A. G. (1963). Congenital aortic stenosis. Clinical and hemodynamic findings in 100 patients. *Circulation,* **27,** 426–462.

Brooksby, I. A. B., Swanton, R. H., Jenkins, B. S., and Webb-Peploe, M. M. (1974). Long sheath technique for introduction of catheter tip manometer or endomyocardial bioptome into left or right heart. *British Heart Journal,* **36,** 908–912.

Buckberg, G., Eber, L., Herman, M., and Gorlin, R. (1975). Ischemia in aortic stenosis: hemodynamic prediction. *American Journal of Cardiology,* **35,** 778–784.

Callard, G. M., Flege, J. B., Jr., and Todd, J. C. (1976). Combined valvular and coronary artery surgery. *Annals of Thoracic Surgery,* **22,** 338–342.

Contratto, A. W., and Levine, S. A. (1937). Aortic stenosis with special reference to angina pectoris and syncope. *Annals of Internal Medicine,* **10,** 1636–1653.

Emanuel, R. (1975). Coronary arteriography. *British Heart Journal,* **37,** 229–230.

Fallen, E. L., Elliott, W. C., and Gorlin, R. (1967). Mechanisms of angina in aortic stenosis. *Circulation,* **36,** 480–488.

Flamm, M. D., Braniff, B. A., Kimball, R., and Hancock, E. W. (1967). Mechanism of effort syncope in aortic stenosis (abstract). *Circulation,* **35-36,** Suppl. II, 109.

Follath, F., and Ginks, W. R. (1972). Changes in the QRS complex after aortic valve replacement. *British Heart Journal,* **34,** 553–560.

Fox, C., Davies, M. J., and Webb-Peploe, M. M. (1973). Length of left main coronary artery. *British Heart Journal,* **35,** 796–798.

Gorlin, R., and Gorlin, S. G. (1951). Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves and central circulatory shunts. *American Heart Journal,* **41,** 1–29.

Harris, C. N., Kaplan, M. A., Parker, D. P., Dunne, E. F., Cowell, H. S., and Ellestad, M. H. (1975). Aortic stenosis, angina, and coronary artery disease. Interrelations. *British Heart Journal,* **37,** 656–661.

Hoffman, J. I. E., and Buckberg, G. D. (1975). Pathophysiology of subendocardial ischaemia. *British Medical Journal,* **1,** 76–79.

Johnson, A. M. (1971). Aortic stenosis, sudden death, and the left ventricular baroreceptors. *British Heart Journal,* **33,** 1–5.

Kennedy, J. W., Trenholme, S. E., and Kasser, I. S. (1970). Left ventricular volume and mass from single plane cineangiocardiogram. A comparison of anteroposterior and right anterior oblique methods. *American Heart Journal,* **80,** 343–352.

Laurent, D., Bolene-Williams, C., and Katz, L. N. (1955). Effects of heart rate on cardiac metabolism. *American Journal of Physiology,* **183,** 638.

Levine, S. A. (1951). *Clinical Heart Disease.* W. B. Saunders, Philadelphia and London.

Lewes, D. (1951). Diagnosis of aortic stenosis based on a study of 25 proved cases. *British Medical Journal,* **1,** 211–216.

Linhart, J. W., de la Torre, A., Ramsey, H. W., and Wheat, M. W., Jr. (1968). The significance of coronary artery disease in aortic valve replacement. *Journal of Thoracic and Cardiovascular Surgery,* **55,** 811–819.

Linhart, J. W., and Wheat, M. W., Jr. (1967). Myocardial dysfunction following aortic valve replacement. The significance of coronary artery disease. *Journal of Thoracic and Cardiovascular Surgery,* **54,** 259–269.

Loop, F. D., Favaloro, R. G., Shirey, E. K., Groves, L. K., and Effler, D. B. (1972). Surgery for combined valvular and coronary heart disease. *Journal of the American Medical Association,* **220,** 372–376.

Mandal, A. B., and Gray, I. R. (1976). Significance of angina pectoris in aortic valve stenosis. *British Heart Journal,* **38,** 811–815.

Merin, G., Danielson, G. K., Wallace, R. B., Rutherford, B. D., and Pluth, J. R. (1973). Combined one stage coronary artery and valvular surgery. *Circulation,* **47-48** Suppl. iii, 173–176.

Mitchell, A. M., Sackett, C. H., Hunzicker, W. J., and Levine, S. A. (1954). The clinical features of aortic stenosis. *American Heart Journal,* **48,** 684–720.

Moraski, R. E., Russell, R. O., Mantle, J. A., and Rackley, C. E. (1976). Aortic stenosis, angina pectoris, coronary artery disease. *Catheterization and Cardiovascular Diagnosis,* **2,** 157–164.

Rodbard, S., Williams, C. B., Rodbard, D., and Berglund, E. (1964). Myocardial tension and oxygen uptake. *Circulation Research,* **14,** 139–149.

Sarnoff, S. J., Braunwald, E., Welch, G. H., Jr., Case, R. B., Stainsby, W. N., and Macruz, R. (1958). Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *American Journal of Physiology,* **192,** 148–156.

Sharratt, G. P., Rees, P., and Conway, W. (1976). Myocardial infarction complicating aortic valve replacement. *The Journal of Thoracic and Cardiovascular Surgery,* **71,** 869–871.

Sonnenblick, E. H., Ross, J., Covell, J. W., Kaiser, C. T., and Braunwald, E. (1965). Velocity of contraction: a major determinant of myocardial oxygen consumption. *Journal of Clinical Investigation,* **44,** 1099.

Wang, Y., Marshall, R. J., and Shepherd, J. T. (1960). The effect of changes in posture and of graded exercise on stroke volume in men. *Journal of Clinical Investigation,* **39,** 1051–1061.

Wood, P. (1958). Aortic stenosis. *American Journal of Cardiology,* **1,** 553–571.

Wood, P. (1968). *Diseases of the Heart and Circulation,* 3rd ed. Eyre and Spottiswoode, London.

Requests for reprints to Dr. R. H. Swanton, Cardiac Department, St. Thomas' Hospital, London SE1 7EH.

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Suppression of refractory arrhythmias by aprindine in patients with the Wolff-Parkinson-White syndrome[1]

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Four patients with supraventricular tachycardia associated with the Wolff-Parkinson-White syndrome were refractory to conventional pharmacological therapy and received aprindine hydrochloride intravenously and orally. Electrophysiological studies disclosed that intravenous aprindine caused increased refractoriness and slowed conduction in the atria, atrioventricular node, ventricles, and accessory pathway. The ability to induce supraventricular tachycardia with timed atrial and ventricular premature stimuli was totally abolished in all 4 patients after intravenous aprindine. Oral aprindine therapy, twice daily thereafter, provided symptomatic relief of the supraventricular tachycardia without significant side effects. Aprindine is useful in the management of supraventricular tachycardia associated with Wolff-Parkinson-White and may offer significant advantages over currently available therapy.

Manifestations of the Wolff - Parkinson - White (WPW) syndrome range from an electrocardiographic curiosity in asymptomatic patients to recurrent, disabling, and life-threatening arrhythmias in others. Worsening of congestive heart failure, precipitation of angina pectoris, and sudden death have been reported in association with the tachyarrhythmias of the WPW syndrome (Wood *et al.*, 1943; Burchell, 1970).

The principle in management of the supraventricular tachycardia is directed toward interruption of the re-entrant circuit which is usually composed of the atrioventricular node, ventricles, accessory pathway, and the atria. Medical management may be aimed at increasing atrioventricular block (vagal stimulation, digitalis, or propranolol) or increasing block in the accessory pathway (quinidine or procainamide). In patients unresponsive to medical therapy, surgical interruption of the atrioventricular node or accessory pathway has been successful (Cobb *et al.*, 1968; Dreifus *et al.*, 1968).

Aprindine (Fasola and Carmichael, 1974) is a new antiarrhythmic agent which may be administered orally or intravenously, with structural similarities to lignocaine and procainamide, but electrophysiological actions resembling quinidine (Elharrar *et al.*, 1975; Steinberg and Greenspan, 1976).

We recently evaluated aprindine hydrochloride in 4 patients with accessory conduction syndromes who were disabled by recurrent supraventricular tachycardia which was refractory to conventional medical management. In these patients, aprindine was initially administered intravenously during an intracardiac electrophysiological study. The acute effects of aprindine on conduction, refractoriness, and induction of supraventricular tachycardia were studied directly. The patients were then placed on oral therapy and followed with Holter monitoring. The response to both intravenous and oral aprindine was nearly complete ablation of the tachyarrhythmias in all 4 patients.

Subjects and methods

Patients were studied unsedated and post-absorptive after informed consent was obtained.

All 4 patients met the criteria for 'therapeutic refractoriness', defined as poor arrhythmic control with therapeutic drug serum levels and/or side effects which precluded continued use of that agent.

All antiarrhythmic drugs were discontinued at least 12 hours before the electrophysiological

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study. Multielectrode catheters were introduced via the antecubital and femoral veins under 1 per cent lignocaine local anaesthesia. A programmable stimulator and constant current isolator which delivered 1 ms impulses at 3 mAmp paced the heart. Catheters were positioned for recording or stimulation at the high right atrium-superior vena caval junction, at the low lateral right atrium, at the apex of the right ventricle, in the coronary sinus, and at the level of the His bundle (Scherlag *et al.*, 1969; Svenson *et al.*, 1974). The lateral coronary sinus position permitted recordings of left atrial potentials. The heart was paced at a constant interval of 600 ms (S_1), and refractoriness was determined by the extrastimulus technique with premature beats (S_2) introduced every eighth beat (Wit *et al.*, 1970). Atrial insertion of the accessory pathway was defined by the sequence of retrograde atrial activation during ventricular pacing. Atrial regions closer to the accessory pathway are activated before the atrial regions which are more distal.

DEFINITION OF TERMS

Effective refractory period (ERP) of atrium: longest atrial S_1 S_2 at which S_2 fails to capture atrium.

AV node ERP: longest A_1 A_2 at which A_2 fails to produce H_2.

Ventricular ERP: longest ventricular S_1 S_2 at which S_2 fails to capture ventricles.

Retrograde accessory pathway ERP: longest V_1 V_2 at which V_2 fails to conduct via the accessory pathway to the atrium.

Premature atrial stimulus re-entry zone: the longest and shortest S_1 S_2 intervals which produced early atrial activation by reciprocation using both AV node and accessory pathway.

Aprindine hydrochloride (molecular weight, 359) was obtained as a lyophilised powder and diluted to 2·8 mmol/l in saline before infusion. After control electrophysiological measurements had been made aprindine was infused intravenously at a dose of 7·8 to 9·7 mmol/kg (2·8 to 3·5 mg/kg) over 15 to 25 minutes. The electrophysiological measurements were repeated 30 minutes after the end of the aprindine infusion. Venous serum samples for aprindine were obtained from the arm not used for drug infusion and analysed by gas liquid chromatography (Murphy, 1974). Aprindine serum levels were expressed as μmol/l of the hydrochloride salt.

All patients with accessory conduction syndromes who were found to be refractory to conventional medical therapy during this study (1975 to 1976) were included in this report. Patients with WPW and adequate arrhythmia control on conventional therapy while in hospital were excluded.

Case reports

CASE 1

A 62-year-old white woman with no significant past or family history had had paroxysmal tachycardia for 11 years. During the tachycardia, she had noted palpitation and weakness without syncope. She frequently fell during the episodes of tachycardia and had fractured her wrist and ribs. Usually the palpitation lasted from several minutes to 6 hours and had resulted in multiple emergency room visits or coronary care unit admissions for electrical cardioversion. In recent years, the frequency of these episodes had increased to several times daily. She denied symptoms of congestive heart failure or angina pectoris. In the 11 years before admission she had been treated with quinidine, digoxin, propranolol, procainamide, and diazepam. Drug side effects and allergies had limited the use of quinidine and procainamide. The use of propranolol and digoxin in combination or alone did not improve arrhythmia control. She was referred for further evaluation.

Physical examination and chest *x*-ray film were normal. A resting 12-lead electrocardiogram showed a regular heart rate of 60 per minute, a PR interval of 0·13 to 0·14 s, a QRS of 0·08 s, and a QT interval of 0·30 to 0·40 s. Frontal and horizontal P and QRS vectors were normal during sinus rhythm. The T wave was inverted in lead V2. Electrocardiograms during spontaneous premature beats or bursts of tachycardia showed QRS widening and suggested the presence of delta waves which were positive in V1.

Electrophysiological study showed evidence for accelerated conduction (Fig. 1). Before aprindine atrial premature beats (from 280 to 500 ms) which encountered delay or block in the AV node conducted with an anomalous pattern identical to the patient's spontaneous premature complexes or tachycardia. The premature atrial stimulus re-entry zone was found to extend from 280 to 320 ms, at a basic cycle length of 600 ms. During the supraventricular tachycardia, the QRS widened, the His potential disappeared, and there was prominent QRS upstroke slurring in V1.

These features suggested anterograde bypass conduction over a left-sided accessory pathway. Thirty minutes after the end of the 150 mg intravenous aprindine the serum level was 2·5 μmol/l (0·9 μg/ml). Atrial refractoriness had increased, the zone of premature atrial (S_2) beats which produced delta waves was eliminated, the re-entry zone was abolished, and no supraventricular tachycardia could be elicited with either premature atrial or

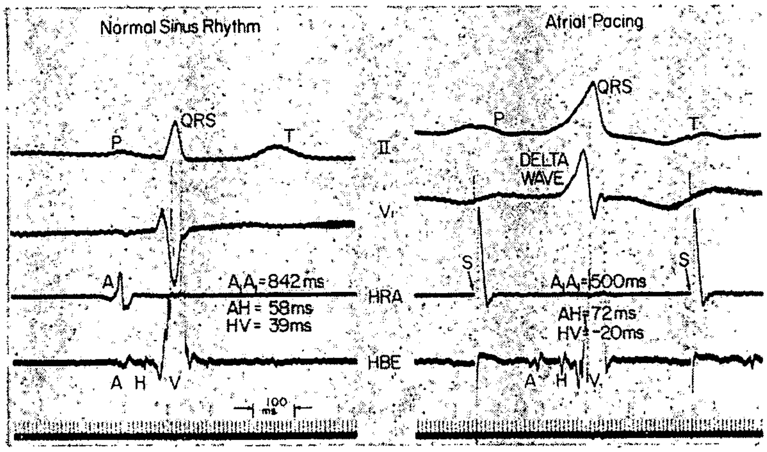

Fig. 1 *Electrograms from case 1. Recorded are surface leads II and V1, high right atrium (HRA), and His bundle electrogram (HBE). In normal sinus rhythm the AH and HV intervals are normal. With rapid atrial pacing, a delta wave appears and the His bundle deflection occurs after the onset of the QRS.*

ventricular stimuli (Table). The dose of 150 mg was not exceeded because the patient noted dizziness without a change in blood pressure or heart rate. The dizziness subsided minutes after stopping the infusion.

Oral aprindine, 25 mg twice daily, was instituted and the patient has not been admitted to hospital or to emergency treatment for 12 months. She occasionally notes palpitation of a few seconds duration. Serum levels on oral aprindine have ranged from 1·3 to 1·9 μmol/l (0·5 to 0·7 μg/ml). Holter monitor recordings have confirmed occasional premature beats without sustained supraventricular tachycardia over 14 months.

CASE 2

A 29-year-old white woman presented with a 19-year history of tachycardia. There was no family history of cardiovascular disease. During three pregnancies, she was admitted to hospital repeatedly for what was described as supraventricular tachycardia. For two years before admission, she noted almost daily episodes of rapid heart rate which were largely unresponsive to vagal manoeuvres. During these episodes, the patient complained of shortness of breath and substernal chest pain. On some occasions, syncopal episodes had resulted in multiple lacerations. The onset of the tachycardia occurred during sleeping or waking hours, usually with a

Table

	Case 1		*Case 2*		*Case 3*		*Case 4*	
Aprindine dose (mg)								
IV (15–25 min)	150		200		200		200	
Oral (per day)	50		100		100		100	
Serum level (μg/ml)								
Acute IV	0·9		2·1		0·9		1·7	
Oral (predose)	0·45–0·7		1·4		1·7		1·9	
Effective refractory period, BCL=600	C	A	C	A	C	A	C	A
Atria	260	450	180	250	250	300	240	230
AV node	<280	<460	<190	<260	<260	400	<250	<240
Ventricles	422	419	310	230	260	250	322	332
Accessory pathway (retrograde)	<432	<429	<320	Block	340	510	<332	<342
Conduction time (ms) BCL=600								
AH	82	85	62	132	129	210	105	120
HV*	38	44	48	89	48	58	0	51
QRS width*	63	88	67	131	88	108	98	89
PAS re-entry zone	280–320	None	190–250	None	260–380	None	250–300	None

C=Control.
A=After aprindine.
BCL=Basic cycle length (ms).
PAS=Premature atrial stimulus.
*Delta wave not present except in Case 4, control, at this BCL.

symptomatic duration from 4 to 5 hours, but occasionally lasting as long as 24 hours.

She had been treated with digitalis, propranolol, and quinidine while in hospital. These drugs alone or in combination at various doses did not prevent the supraventricular tachycardia.

Physical examination, chest *x*-ray film, and echocardiogram were normal. The resting electrocardiogram showed sinus rhythm at 70 per minute, a PR interval of 0·14 s, and a QRS duration of 0·08 s. Holter monitoring before electrophysiological study revealed frequent episodes of a regular supraventricular tachycardia with normal QRS duration, no delta waves, and P waves which were difficult to identify. Multiple previous Holter monitoring recordings disclosed bursts of supraventricular tachycardia at rates of 140 to 200 per minute, which were frequently initiated by an atrial premature beat. At lower rates, the tachycardia was regular, but at higher rates, P waves could not be identified and gross irregularity developed, raising the question of atrial fibrillation.

Electrophysiological study (Fig. 2) showed that the paroxysmal tachycardia involved anterograde conduction through the AV node and bundle-branches and retrograde conduction via an accessory bundle located in the lateral mitral valve ring. Thirty minutes after the end of intravenous infusion of 200 mg aprindine serum levels were 5·8 μmol/l (2·1 μml). Atrial effective refractory period had increased, while complete retrograde block was produced in the accessory conduction bundle (anterograde conduction could never be shown, either before or after aprindine). Aprindine eliminated the re-entry zone (190 to 250 ms before aprindine). After aprindine, the tachycardia could not be produced with any interval of prematurity (Table). Atrial pacing at 3 progressively more rapid basic cycle lengths until Wenckebach AV conduction appeared and ventricular pacing at 5 different basic cycle lengths likewise failed to induce re-entry.

Oral aprindine, 50 mg twice daily, gave excellent control of arrhythmias with predose serum levels of 3·9 μmol/l (1·4 μg/ml). Holter monitoring confirmed that occasional premature beats were present without sustained supraventricular tachycardia.

CASE 3

A 67-year-old white man was referred for evaluation of recurrent episodes of palpitation. The patient survived a myocardial infarction 16 years before admission. Twelve years before admission, he noted palpitation of abrupt onset associated with weakness, diaphoresis, light-headedness, and shortness of breath. Three years before admission an inferior myocardial infarction was complicated by ventricular fibrillation. Symptoms of palpitation and weakness without syncope had progressively increased over the 4 to 5 years before admission with up to 4 episodes a day lasting from minutes to hours. Digitalis was increased to toxicity. Propranolol was limited to 80 mg daily because of lethargy, depression, and dyspnoea. The patient had no benefit from phenytoin at 300 to 400 mg per day. Quinidine produced intractable diarrhoea, and procainamide caused a skin rash and fever. The patient was referred for further evaluation.

Physical examination revealed an S_4 gallop rhythm without cardiomegaly. Chest *x*-ray film was normal. The electrocardiogram during sinus rhythm showed Q waves in II, III, and aVF, and T wave inversion in II, III, and aVF and V6 (Fig. 3). During the frequent tachycardia noted on Holter monitoring, P waves could not be identified, and the ventricular rate was 140 to 160 per minute, regular, with unchanged QRS complexes. Delta waves were absent on most tracings, but on some electrocardiograms delta waves were seen to be positive in lead V1.

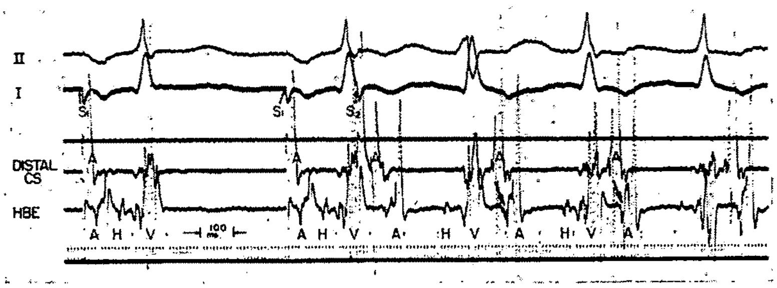

Fig. 2 *Electrograms from case 2. Recorded are surface leads II and I, distal coronary sinus (distal CS, in the lateral mitral valve ring), and His bundle electrogram (HBE). Pacing at a constant cycle length ($S_1S_1=600$ ms), an S_2 introduced at $S_1S_2=210$ ms initiates supraventricular tachycardia with anterograde conduction through the His bundle (normal HV), retrograde conduction through an accessory pathway with early activation of distal coronary sinus. Initial QRS of tachycardia conducts aberrantly with leftward axis shift. Large arrows (fourth and fifth atrial complexes) show spread of atrial activation from distal coronary sinus to low right atrium (recorded in HBE).*

Electrophysiological study (Fig. 4) indicated an accessory conduction pathway located laterally in the mitral valve ring which was active retrogradely but silent anterogradely. Intravenous aprindine, 200 mg, increased the atrial and retrograde accessory pathway effective refractory period. Before aprindine, appropriately timed atrial premature beats (260–380 ms) induced the supraventricular tachycardia. The re-entry zone had been eliminated and supraventricular tachycardia could not be pro-

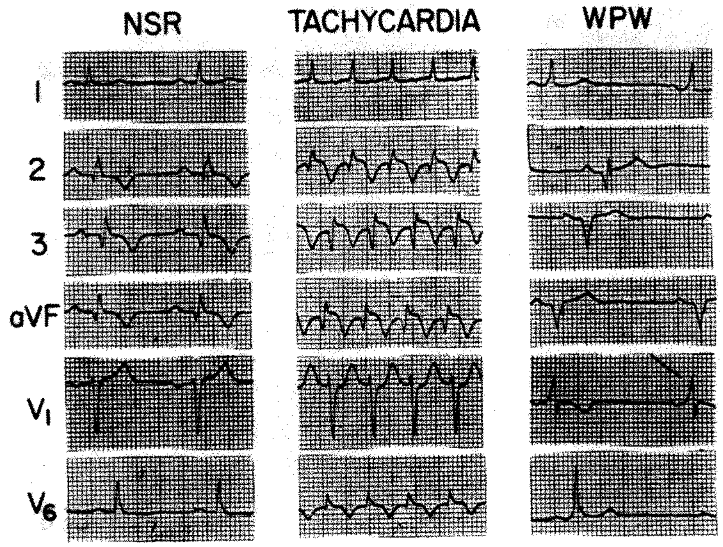

Fig. 3 *Electrocardiograms of case 3. NSR (left column) : normal sinus rhythm with Q waves of previous infarct and absent delta waves. Tachycardia (middle column) : QRS complex unchanged during SVT and consistent with anterograde conduction through the AV node, His bundle and bundle branches. WPW (right column) : occasionally (often at heart rates less than 60/minute) delta waves appeared suggesting type A WPW.*

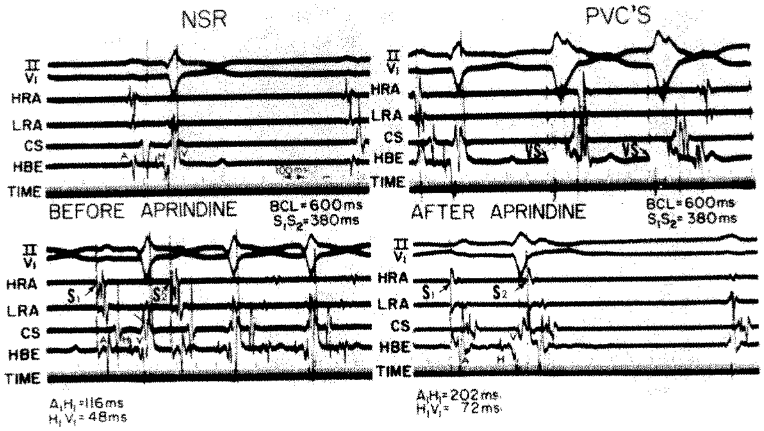

Fig. 4 *Intracardiac recording and stimulation performed on case 3. NSR (upper left panel) : during normal sinus rhythm, multiple atrial catheters permit mapping of atrial sequence of activation. II, V1 = standard surface electrocardiograms; HRA = high right atrium; LRA = low right atrium; CS = coronary sinus in lateral mitral valve ring; HBE = His bundle electrogram; A = atrial deflection; H = His bundle deflection; V = ventricular deflection. Atrial sequence proceeds from high to low atrium with coronary sinus potentials occurring last.*

Premature ventricular contractions (upper right panel) : same format as upper left panel. Premature ventricular stimuli (VS) induce premature ventricular contractions (PVCs). Sequence of retrograde atrial activation is recorded with coronary sinus potential occurring first, suggesting retrograde conduction via the accessory pathway located in the mitral valve ring.

Before aprindine (lower left panel) : at basic cycle length (BCL) of 600 ms (S_1), a premature atrial stimulus (S_2) introduced at 380 ms induces the supraventricular tachycardia with the atrial activation sequence producing early potentials in the coronary sinus. This sequence suggests that the premature impulse conducts anterogradely in the normal pathway but conducts retrogradely through the accessory pathway in the mitral valve ring.

After aprindine (lower right panel) : at same basic cycle length of 600 ms (S_1) a premature atrial stimulus (S_2) introduced at 380 ms blocks in its anterograde progression in both the AV node and the accessory pathway. Therefore, no tachycardia ensues. Note that A_1 H_1 and H_1 V_1 are prolonged after aprindine, and QRS width has increased.

duced 30 minutes after the end of the aprindine infusion. Atrial pacing at four progressively more rapid basic cycle lengths, to the point of Wenckebach AV block, and ventricular pacing at one basic cycle length failed to induce re-entry. The serum level at this time was 2·5 µmol/l (0·9 µ/ml).

Oral aprindine, 50 mg twice daily, produced serum levels of 4·7 µmol/l (1·7 µg/ml) and prevented symptomatic attacks of supraventricular tachycardia. Holter monitoring during 3 months of follow-up evaluation confirmed the absence of supraventricular tachycardia.

CASE 4

A 50-year-old white woman had a 35-year history of paroxysmal supraventricular tachycardia. The episodes of supraventricular tachycardia had required several admissions to hospital and electrical cardioversion, though many episodes of supraventricular tachycardia were aborted at home using vagal manoeuvres. An electrophysiological study at the age of 49 showed a left-sided accessory pathway and a patent foramen ovale. With combinations of digitalis, propranolol, procainamide, and quinidine, the episodes of supraventricular tachycardia requiring admission to hospital were reduced from 5 to 6 to 2 to 3 times per year. Higher doses of these drugs resulted in intolerable gastrointestinal side effects probably associated with a hiatal hernia and reflux oesophagitis. Symptoms during these periods included near syncope or syncope, chest pain, and shortness of breath. Her most recent admission to hospital was prompted by palpitation, substernal chest pain, and near syncope. During this admission, she was referred for further evaluation.

Her physical examination disclosed obesity and diffuse expiratory wheezes. The chest *x*-ray film showed a normal cardiac silhouette and basilar pulmonary fibrosis without infiltrates. The resting 12-lead electrocardiogram showed sinus rhythm, a PR interval of 0·12 s, minor nonspecific ST-T changes, a QRS duration of 0·12 s, and a delayed initial R upstroke consistent with delta waves. The delta waves were most prominent in II, III, aVF, V1–3. During the supraventricular tachycardia ventricular rates ranged from 180 to 215 per minute, delta waves disappeared, and P waves could not be identified while ST segments became more deeply depressed.

With a repeat electrophysiological study (Fig. 5) the presence of an accessory pathway near the lateral mitral ring was confirmed. Atrial premature beats (S_2) from 250–580 ms produced delta waves and identified a premature atrial stimulus re-entry zone of 250 to 300 ms (Table). During the supraventricular tachycardia, delta waves disappeared, the HV interval lengthened to normal, and early retrograde left atrial activation identified a left-sided active accessory pathway. The patient received 200 mg aprindine intravenously over 20 minutes. Thirty minutes after the end of the infusion, delta waves were still present at the basic cycle length of 600 ms and atrial (S_2) prematurity levels from 580 to 240 ms. However, the premature atrial stimulus re-entry zone had been abolished and supraventricular tachycardia could no longer be induced. Re-entry was not seen with atrial pacing and premature stimuli at two basic cycle lengths from both right and left atria and ventricular pacing at two basic cycle lengths. The aprindine serum level at this time was 4·7 µmol/l (1·7 µg/ml).

Twenty-four hours later, the patient was placed

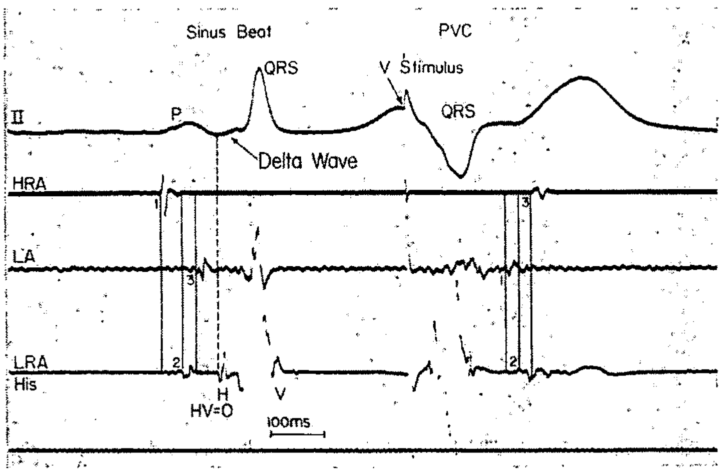

Fig. 5 *Electrograms from case 4. Recorded are surface lead II, high right atrium (HRA), left atrium (LA, recorded with a catheter positioned at the lateral mitral valve ring across a patent foramen ovale), and His bundle tracing (LRA-His). Sinus P wave conducts with an atrial sequence from HRA (1) to LRA (2) to LA (3). An induced premature ventricular beat (PVC) with a ventricular pacing catheter (V stimulus) conducts retrogradely with early atrial activation in the lateral LA (1), then activation of low RA (2) and finally high RA (3). This sequence of retrograde atrial activation confirms the presence of a left-sided bypass pathway.*

on oral aprindine at a dose of 50 mg every 12 hours. Predose levels were found to be 5·3 µmol/l (1·9 µg/ml). The patient noted a decrease in the frequency of palpitation with no sustained tachycardia. Repeated 24-hour Holter monitoring during a 5-month follow-up period confirmed the absence of sustained tachycardias.

Discussion

Aprindine is a tertiary amine with local anaesthetic properties making it similar to lignocaine. However, the half-life (20 to 30 hours) is much longer, and oral absorption confers effective antiarrhythmic activity (Fasola and Carmichael, 1974; Murphy, 1974). Therapeutic blood levels have been estimated to be 2·8–5·6 µmol/l (1–2 µg/ml) (Fasola and Carmichael, 1974). The side effects are primarily in central nervous system and include dizziness, tremor, nystagmus, and ataxia. These side effects disappear when the dose is reduced or stopped.

Experimental studies in animals have indicated that aprindine increased the effective refractory period and conduction time in the atrium, AV node, and distal conduction system (Elharrar *et al.*, 1975; Steinberg and Greenspan, 1976).

Acute administration of aprindine increased atrial effective refractory period in 3 of the 4 patients (Table). Measurement of AV node anterograde effective refractory period was limited by atrial effective refractory period in 2 cases, though AV node effective refractory period unequivocally increased in 1 patient. AV node conduction time (AH interval) increased significantly in 3 of the 4 patients.

Anterograde accessory pathway conduction was seen in only cases 1 and 4. After aprindine the anterograde refractoriness increased in 1 of these 2 patients (case 1).

After aprindine, retrograde refractoriness of the accessory pathway was increased or complete block was produced in 2 of the 4 patients (cases 1 and 4) In the remaining 2 cases, right ventricular effective refractory period was reached before that of the accessory pathway.

The His-Purkinje conduction time (HV interval) and QRS duration increased transiently in 3 of the 4 patients. These intervals returned toward normal by the end of the study, suggesting that aprindine should be given as a slow infusion to avoid a potential dose-related distal conduction delay. In case 4, at the basic cycle length of 600 ms, a delta wave was present before aprindine and not after aprindine, producing a QRS shortening and HV lengthening caused by more normal antegrograde conduction. The refractoriness of the ventricles was unchanged in 3 patients and appeared to shorten in 1 patient. The apparent shortening of the ventricular refractoriness may represent some instability of catheter position in this 1 patient. The finding of no change in refractoriness in the other 3 patients is more consistent with animal studies which show small dose-related increases in ventricular effective refractory period.

At a constant basic cycle length of 600 ms, the atrial premature beat interval which induced supraventricular tachycardia—the 're-entry zone'—was abolished in all 4 patients. The increased conduction time and refractoriness of the atria, the accessory pathway, and possibly the AV node, appear to account for the effective results with aprindine.

When begun on oral therapy, all patients became asymptomatic from their previously disabling supraventricular tachycardia. The symptomatic improvement was subsequently confirmed by repeated Holter monitoring while the patients were ambulatory.

It is noteworthy that all these patients had left-sided accessory pathways. Since the study group is small and no refractory WPW patients were eliminated from this study it cannot be determined whether or not this finding is coincidental or represents some special predilection of patients with left-sided pathways to drug resistance.

In man, aprindine has been used primarily to control ventricular arrhythmias (Kesteloot *et al.*, 1973; Hagemeijer *et al.*, 1974). Aprindine has been used less frequently for supraventricular tachycardia, though a few patients have been reported in whom it was effective for supraventricular tachycardia associated with WPW syndrome (Kesteloot *et al.*, 1973; Kesteloot, 1974; Fasola and Carmichael, 1974; Neuss and Schlepper, 1974; Palma-Gamiz *et al.*, 1974). Aprindine appears effective against the refractory supraventricular tachycardia associated with the WPW syndrome because it eliminates re-entry zones by slowing conduction and increasing refractoriness in the cardiac tissues which initiate or perpetuate the supraventricular tachycardia. While similar changes may be seen with quinidine and procainamide, the magnitude of the effect by aprindine on different parts of the re-entrant loop may permit better arrhythmia control at doses which do not produce unacceptable side effects.

Other new antiarrhythmic agents, such as amiodarone (Rosenbaum *et al.*, 1974), have also been successfully used in WPW patients. The mechanism of action of amiodarone is similar to aprindine in slowing conduction but has other effects such as a coronary vasodilatation and catecholamine antagonism which may be important in producing antiarrhythmic effects.

It would not be expected that aprindine will be successful in all therapeutically refractory WPW patients. However, these preliminary results are encouraging, and the long half-life (permitting dosing twice daily) with possibly fewer side effects, should improve patient compliance. These features may offer improved patient management with reduced requirement for surgical or other invasive procedures.

References

Burchell, H. B. (1970). Surgical approach to the treatment of ventricular pre-excitation. *Advances in Internal Medicine,* **16,** 43–58.

Cobb, F. R., Blumenschein, S. D., Sealy, W. C., Boineau, J. P., Wagner, G. S., and Wallace, A. G. (1968). Successful surgical interruption of the bundle of Kent in a patient with Wolff-Parkinson-White syndrome. *Circulation,* **38,** 1018–1029.

Dreifus, L. S., Nichols, H., Morse, D., Watanabe, Y., and Truex, R. (1968). Control of recurrent tachycardia of Wolff-Parkinson-White syndrome by surgical ligature of the AV bundle. *Circulation,* **38,** 1030–1036.

Elharrar, V., Foster, P. R., and Zipes, D. P. (1975). Effects of aprindine HCl on cardiac tissues. *Journal of Pharmacology and Experimental Therapeutics,* **195,** 201–205.

Fasola, A. F., and Carmichael, R. (1974). The pharmacology and clinical evaluation of aprindine, a new antiarrhythmic agent. *Acta Cardiologica,* **29,** Suppl. 18, 317–333.

Hagemeijer, F., Janse, C., and Hugenholtz, P. G. (1974). Efficacite antiarthythmique de l'aprindine a la phase aiguë de l'infarctus du myocarde. *Acta Cardiologica,* **29,** Suppl. 18, 409–421.

Kesteloot, H. (1974). General aspects of antiarrhythmic treatment with aprindine. *Acta Cardiologica,* **29,** Suppl. 18, 303–316.

Kesteloot, H., Van Mieghem, W., and DeGeest, H. (1973). Aprindine (AC 1802) a new antiarrhythmic drug. *Acta Cardiologica,* **28,** 145–165.

Murphy, P. J. (1974). Metabolic pathways of aprindine. *Acta Cardiologica,* **29,** Suppl. 18, 131–142.

Neuss, H., and Schlepper, M. (1974). Influence of various antiarrhythmic drugs (aprindine, ajmaline, verapamil, oxprenolol, orciprenaline) on functional properties of accessory AV pathways. *Acta Cardiologica,* **29,** Suppl. 18, 279–288.

Palma-Gamiz, J. L., Boedo, C., Lopez-Pujol, F. J., and de Uria, J. S. (1974). Etude clinique d'un nouvel antiarythmique: aprindine. *Acta Cardiologica,* **29,** Suppl. 18, 361–368.

Rosenbaum, M. B., Chiale, P. A., Rybe, D., and Elizari, M. V. (1974). Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride. *American Journal of Cardiology,* **34,** 215–223.

Scherlag, B. J., Lau, S. H., Helfant, R. H., Berkowitz, W. D., Stein, E., and Damato, A. N. (1969). Catheter technique for recording His-bundle activity in man. *Circulation,* **39,** 13–18.

Steinberg, M. I., and Greenspan, K. (1976). Intracellular electrophysiological alterations in canine cardiac conducting tissue induced by aprindine and lignocaine. *Cardiovascular Research,* **10,** 236–244.

Svenson, R. H., Gallagher, J. J., Sealy, W. C., and Wallace, A. G. (1974). An electrophysiologic approach to the surgical treatment of the Wolff-Parkinson-White syndrome. *Circulation,* **49,** 799–804.

Wit, A. L., Weiss, M. B., Berkowitz, W. D., Rosen, K. M., Steiner, C., and Damato, A. N. (1970). Patterns of atrioventricular conduction in the human heart. *Circulation Research,* **27,** 345–359.

Wood, F. C., Wolferth, C. C., and Geckeler, G. D. (1943). Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short PR interval and prolonged QRS complex. *American Heart Journal,* **25,** 454–462.

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Simple lignocaine regimen for transit to hospital after myocardial infarction

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A simple combined intravenous/intramuscular regimen is described for lignocaine administration in the early vulnerable stage of myocardial infarction. Plasma levels in the therapeutic range are attained. This allows adequate drug protection during transport to hospital when an intravenous regimen may be impractical or impossible.

Lignocaine remains the first line of attack against ventricular arrhythmia after myocardial infarction. Plasma levels required for this purpose are said to lie between 6·4 and 21 μmol/l (1·5 to 5 μg/ml) (Harrison and Alderman, 1971; Collinsworth *et al.*, 1974; Koch-Weser, 1975; Aps *et al.*, 1976). There is difficulty in maintaining adequate plasma concentrations in the first two hours of treatment using conventional intravenous dosage (Aps *et al.*, 1976). If such treatment is started in the patient's home, he is likely to be denied protection from arrhythmias at a time when the risk is greatest and surveillance most difficult.

We report our experience using a simple combination of an intravenous bolus and intramuscular injection as a means of overcoming these difficulties.

Methods

Twelve consecutive patients admitted to the Coronary Care Unit, who fulfilled our criteria for lignocaine therapy (Walsh *et al.*, 1972) and who had not received any antiarrhythmic drug outside hospital, received the combined intravenous/intramuscular regimen. Two patients were excluded subsequently because of technical problems relating to the timing of samples for estimation of drug concentration. Of the remaining 10, 8 were men and 2 women, and their ages varied from 28 to 74 years. One patient (case 9) had mitral stenosis and was in heart failure. All the remainder had had a myocardial infarct and one of these (case 8) also had pulmonary venous congestion. Their weights varied from 55·3 to 76·7 kg. The electrocardiograms of these patients were recorded continuously by a direct-writing electrocardiograph over a 4-hour period and blood pressure was recorded at 15-minute intervals. The recordings were scanned by two observers for changes in heart rate or rhythm.

The patients were given 100 mg lignocaine hydrochloride by intravenous injection over 2 minutes into an arm vein. Five minutes after the beginning of the intravenous injection, 300 mg were given by intramuscular injection into the deltoid muscle. The time of the intramuscular injection was taken as zero time and 10 ml blood samples were taken from a vein in the other arm 2 minutes before zero time and then at 3, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, and 240 minutes. The blood was centrifuged and stored at 4°C until plasma concentrations were estimated.

Plasma lignocaine was estimated by a gas chromatographic method. One ml samples of plasma, containing diphenhydramine 5 μg as an internal standard, were made alkaline with 0·5 ml of 2M NaOH. Samples were extracted with 5 ml portions of ether. The ether layer was removed and evaporated to dryness. Samples were reconstituted with 30 μl portions of dichloromethane and 1 μl portions injected into a gas chromatograph (Perkin-Elmer model F11) fitted with a flame-ionisation detector. The column was glass, 6 ft in length and 0·25 in outer diameter and was packed with 2 per cent carbowax 20M on KOH treated chromosorb G. Oven temperature was 200°C and nitrogen carrier gas flow rate was 40 ml/min. The relative retention time of lignocaine to diphenhydramine was 1·4.

Drug half-life ($t\frac{1}{2}$) was estimated from the terminal portion of the plasma curves by least squares regression analysis. The data from 60 to 240 minutes

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was used (45 to 240 minutes for case 8). The area under the plasma concentration/time curve was estimated using the trapezoidal rule, and drug clearance (dose/area) calculated, assuming that all the drug from the intramuscular injection site had been absorbed and therefore that the total systemic dose was 400 mg. The volume of distribution (Vd) was derived from the equation:

$$\text{Clearance} = \text{Vd}.\beta, \text{ where } \beta = \frac{0{\cdot}693}{t_{\frac{1}{2}}}.$$

Results

No patient developed symptomatic or haemodynamic side effects during the 4-hour period of observation. One patient (case 3) required further lignocaine for recurrent arrhythmia soon after the 4-hour period was over.

The Table and Figure summarise plasma lignocaine concentrations found in the patients. In only one patient did the plasma level fall below 6·4 µmol/l (1·5 µg/ml) in the first 2 hours. At 4 hours, only 4 patients had plasma levels above 6·4 µmol/l (1·5 µg/ml).

The mean drug half-life was 136·2 ± 29·3 minutes with a mean lignocaine clearance of 507 ml/min and volume of distribution of 82 litres. The range of values are shown in the Table.

Discussion

In myocardial infarction the commonest cause of death is ventricular arrhythmia occurring in the early phase of the attack (Pantridge and Geddes, 1967). The generally accepted first line drug to counter this is lignocaine and there is some clinical evidence that its early use may lower mortality (Morgensen, 1970; Valentine *et al.*, 1974).

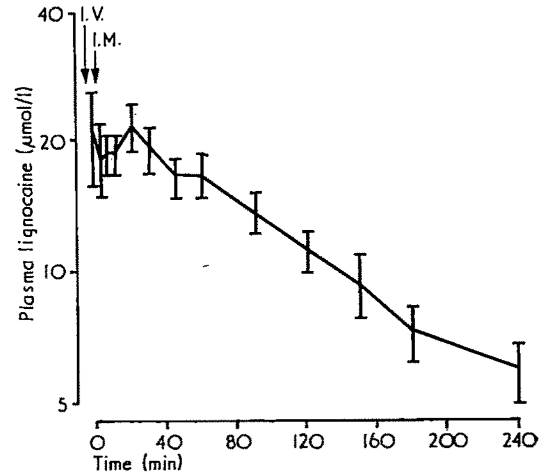

Fig. *Mean plasma lignocaine concentrations after the administration of lignocaine 100 mg intravenously at −3 minutes and 300 mg intramuscularly at time 0. Results are mean of 10 patients ± SEM.*

The usual lignocaine regimen is an intravenous bolus of 1 to 2 mg/kg, followed by constant infusion of 1 to 4 mg/min. Aps *et al.* (1976) have emphasised that this is associated with a period of about 2 hours when the plasma concentration is subtherapeutic and have recommended a more complex regimen involving different and reducing rates of infusion. We have found that meticulous control of intravenous infusion flow rates is very difficult during travel in an ambulance and an alternative seemed desirable. The combination of an intravenous bolus and intramuscular injection was a possible answer, and we were pleased to find that in all our patients therapeutic levels were maintained long enough to allow transport from home to hospital. The mean plasma concentrations in the first two hours of treatment were similar to those re-

Table *Plasma lignocaine concentrations and pharmacokinetic measurements after intravenous/intramuscular lignocaine*

	Plasma lignocaine concentration (µmol/l)													*t½ (min)*	*β (min⁻¹)*	*Clearance (ml/min)*	*Vd (l)*
	−2 (min)	*3*	*5*	*10*	*20*	*30*	*45*	*60*	*90*	*120*	*150*	*180*	*240 (min)*				
1	29·0	17·5	18·8	22·2	17·9	22·6	17·5	21·8	18·3	15·8	16·2	10·7	6·8	114·5	0·0062	669	108
2	11·5	16·6	10·2	17·9	20·1	18·3	15·8	17·9	19·2	11·9	7·3	4·3	4·3	71·7	0·0096	540	56
3	25·2	—	26·5	23·9	22·6	16·2	12·8	16·6	11·9	9·4	6·8	5·5	3·8	86·0	0·008	553	69
4	46·5	—	19·2	—	25·6	16·6	23·0	22·2	13·7	—	10·2	6·4	5·1	88·5	0·0078	440	56
5	29·0	13·2	18·3	15·8	19·2	14·9	12·8	11·9	15·8	14·1	11·9	11·9	8·5	177·1	0·0039	511	80
6	19·2	42·7	—	—	40·5	32·9	27·3	23·0	17·1	14·5	16·6	10·7	10·7	177·1	0·0039	334	60
7	5·5	16·6	13·7	13·2	24·3	23·0	17·9	18·8	15·8	11·9	5·5	5·1	4·3	75·3	0·0092	537	58
8	47·8	12·8	21·8	25·3	20·1	24·7	11·9	—	0·8	7·3	5·5	5·1	—	103·8	0·0066	591	90
9	4·3	18·8	25·6	18·8	15·4	11·1	12·8	7·7	6·0	5·1	3·0	2·6	2·1	91·2	0·0075	733	98
10	2·1	9·8	13·7	12·8	13·2	11·5	13·2	11·5	9·4	9·0	9·8	8·5	7·7	376·3	0·0018	257	142
Mean	22·0	18·5	18·6	18·7	21·9	19·2	16·5	16·8	13·7	11·0	9·3	7·1	5·9	136·2	0·0064	507	82
SEM	5·2	3·6	1·8	1·7	2·4	2·1	1·6	1·8	1·4	1·2	1·4	1·0	0·9	29·3	0·0008	51	9

Conversion: SI to traditional units—lignocaine: 1 µmol/l ≃ 0·23 µg/ml.

ported by Aps *et al.* (1976) using his more complicated regimen. Most lethal arrhythmias occur in the first few hours after the onset of myocardial infarction, so that in many patients no further antiarrhythmic drug may be needed after receiving the combined intravenous/intramuscular lignocaine. However, the main practical advantage of the combination is that it ensures adequate plasma concentration in the early vulnerable phase while the patient is being transported to hospital, whether by specially equipped ambulance or not.

We cannot say if the doses we have used would be appropriate in patients with severe shock or heart failure who may handle the drug differently, but these complications rarely occur during the very early phase of the attack. Certainly, the estimates of half-life, clearance, and volume of distribution of lignocaine obtained in this present study appear to lie somewhere between those previously found after constant intravenous infusion in normal volunteers (Boyes *et al.*, 1971) and in patients after myocardial infarction (Prescott and Nimmo, 1971).

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References

Aps, C., Bell, J. A., Jenkins, B. S., Poole-Wilson, P. A., and Reynolds, F. (1976). Logical approach to lignocaine therapy. *British Medical Journal,* **1,** 13–15.

Boyes, R. N., Scott, D. B., Jebson, P. J., Godman, M. J., and Julian, D. G. (1971). Pharmacokinetics of lidocaine in man. *Clinical Pharmacology and Therapeutics,* **12,** 105–116.

Collinsworth, K. A., Kalman, S. M., and Harrison, D. C. (1974). The clinical pharmacology of lidocaine as an antiarrhythmic drug. *Circulation,* **59,** 1217–1230.

Harrison, D. C., and Alderman, E. L. (1971). Relation of blood levels to clinical effectiveness of lidocaine. In *Lidocaine in the Treatment of Ventricular Arrhythmias,* p. 178. Ed. by D. B. Scott and D. G. Julian. Livingstone, Edinburgh and London.

Koch-Weser, J. (1975). Drug interactions in cardiovascular therapy. *American Heart Journal,* **90,** 93–116.

Morgensen, L. (1970). Ventricular tachyarrhythmias and lignocaine prophylaxis in acute myocardial infarction. A clinical and therapeutic study. *Acta Medica Scandinavica,* Suppl. 513.

Pantridge, J. F., and Geddes, J. S. (1967). A mobile intensive-care unit in the management of myocardial infarction. *Lancet,* **2,** 271–273.

Prescott, L. F., and Nimmo, J. (1971). Plasma lidocaine concentrations during and after prolonged infusions in patients with myocardial infarction. In *Lidocaine in the Treatment of Ventricular Arrhythmias,* p. 168. Ed. by D. B. Scott and D. G. Julian. Livingstone, Edinburgh and London.

Valentine, P. A., Frew, J. L., Mashford, M. L., and Sloman, J. G. (1974). Lidocaine in the prevention of sudden death in the pre-hospital phase of acute infarction. A double blind study. *New England Journal of Medicine,* **291,** 1327–1331.

Walsh, M. J., Shivalingappa, G., Scaria, K., Morrison, C., Kumar, B., Farnan,C.,Chaturvedi, N. C., Boyle, D. McC., and Barber, J. M. (1972). Mobile coronary care. *British Heart Journal,* **34,** 701–704.

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Longevity of programmable energy output pacemakers
Early results and experiences[1]

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To solve the problem of pacemaker longevity, current output, and pulse width programmable pacing systems were introduced for clinical use in 1972. Thirty-seven patients with such systems were serially assessed in our pacemaker follow-up clinic for an average of 23 months (range 6 to 36 months). Twenty-five patients received the Cordis Omnicor system (programmable current output), while 12 patients received the Medtronic 5961 system (programmable pulse width). Pacemaker failure caused by battery exhaustion occurred in 5 Omnicor units (average 29·0 months) with an average current output of 4·8 mA in 4. One Medtronic 5961 unit failed after 19 months (0·8 ms pulse width) because of a manufacturing defect in the battery sealing. The 31 remaining programmable pacers remain functional (average 22 months). Special problems encountered included increased early incidence of cardiac perforation attributable to small surface area endocardial electrodes (6 patients); ventricular fibrillation induced by unipolar fixed rate pacing (2 patients) representing the first report of cathode provoked ventricular tachyarrhythmias caused by the R on T phenomenon and pacemaker vulnerability to direct current countershock resulting in fixed rate pacing (1 patient). Despite lack of sufficient prolongation of pacemaker life, unique advantages of the programmable systems constitute ability to alter heart rate to allow evaluation of patients' intrinsic rhythm and QRS complexes, overdrive suppression of ventricular tachyarrhythmias, and determination of chronic threshold and early detection of exit block. This experience to date with the programmable Omnicor system does not appear to provide improved pacemaker lifetime compared with our 22 nonprogrammable Cordis and Medtronic demand pacemakers with an average longevity of 31·5 months. Attention to alternate power sources such as lithium iodide batteries may be a more promising approach to increasing pacemaker life.

It is generally agreed that battery depletion is the primary limiting factor in the service life of permanent pacemakers. Since battery depletion is a function of the amount of energy delivered by the pulse generator, reducing this energy expenditure should allow extension of functional pacemaker life. Standard pacemakers in current use contain four or five mercury-zinc cells each with a capacity of 1000 mA–h and a maximum pacemaker output of 9 to 11 milliamperes. Cardiac thresholds for chronic stimulation in the majority of patients are usually low and average 1·6 milliamperes at a pulse width of 1·0 ms (Furman *et al.*, 1975). Therefore, the constant delivery of 9 to 11 milliamperes of current by permanent pacemakers constitutes considerably more expenditure of energy output than is necessary for chronic stimulation in most patients and thereby results in rapid depletion of pacemaker batteries. The recent advent of programmable pacemakers (Chardack *et al.*, 1971; Morse *et al.*, 1975) allows serial assessment of the patient's chronic stimulating threshold. Thus, pacemaker output can be adjusted to deliver sufficient energy for constant chronic pacing, thereby conserving energy and enhancing functional pacemaker life.

Pacemaker energy output is represented by the product of voltage, current, and pulse duration. Therefore, energy conservation can be affected either by decreasing current output delivered to the

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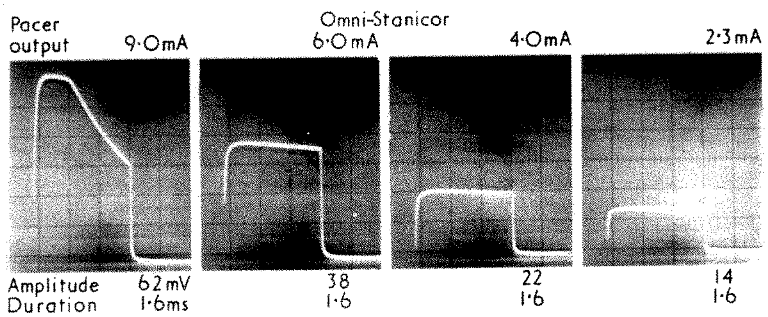

Fig. 1 *Representative oscilloscopic recordings of the configuration and amplitudes of the pacemaker artefact obtained at the different pacemaker output settings from an Omni-Stanicor programmable pacemaker. At a maximum output of 9 milliampres (mA) (high setting), the artefact has the shape of a truncated rectangle. As the output is diminished from 9 to 6 mA (medium setting), the artefact amplitude decreases and the shape becomes rectangular. As the output setting is further decreased to 4 mA (low setting) and then to 2·3 mA (test setting), the amplitude declines further. 1 vertical square = 10 millivolts (mV); 1 horizontal square = 0·5 millisecond (ms). The pulse duration is unaffected by change in current output.*

heart while keeping pulse width constant (Fig. 1) or by decreasing the duration of current delivery while maintaining current constant (Fig. 2). The former technique has been employed by one pacemaker manufacturer (Cordis Corporation, Miami, Florida) with programmable current output pacemakers identified as the 'Omni' series (Omnicor). The alternative approach is the pulse width controllable pacemakers, which are manufactured by the Medtronic Company (Minneapolis, Minnesota). It is the purpose of this study to evaluate the longevity of these two different externally programmable pacemaker systems relative to the life span of standard demand pacemakers manufactured by the respective companies.

Methods and Materials

A total of 128 patients with permanent pacemakers was evaluated, 56 with programmable demand systems and 72 with standard demand pacemakers. Thirty-two patients received the Omnicor programmable pacemaker and 8 received nonprogrammable Cordis units. Twenty-four patients had the programmable Medtronic 5961 system and 64 the nonprogrammable demand Medtronic units. All 128 patients were serially followed in the pacemaker evaluation clinic for 0·5 to 4·1 years (mean 2·7 years). It is ideal to follow a large group of patients over several years until the majority of pacemakers fail. This allows a definite assessment of longevity

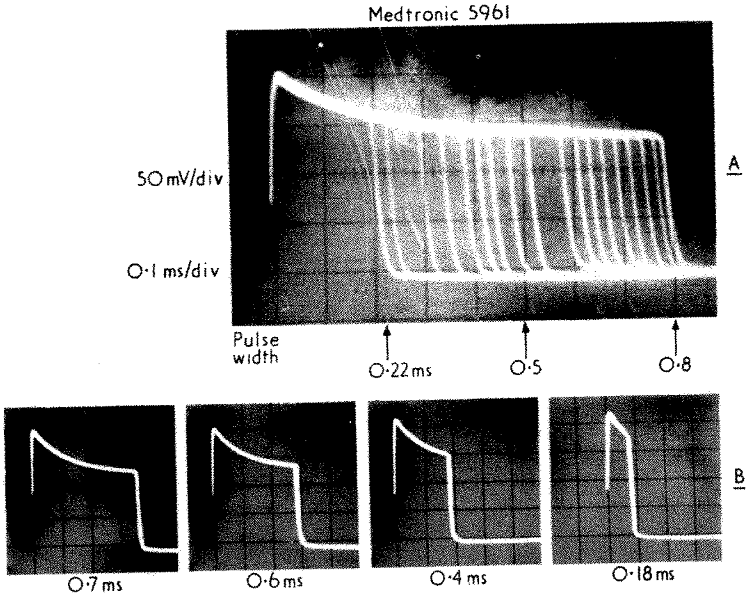

Fig. 2 *(A) Representative oscilloscopic recordings illustrating the process of narrowing of pulse width of a programmable Medtronic unit (Model 5961). Starting with the pulse width of 0·8 ms, the external pulse width controller was activated with gradual decrease of pulse width ultimately to 0·22 ms. The simultaneously monitored electrocardiogram with the change in pulse width showed that there was no loss of pacemaker capture. 1 vertical square (div) = 50 mV; 1 horizontal square = 0·1 ms. (B) Representative recordings showing isolated pacemaker artefacts at different pulse width settings. 1 vertical square = 50 mV; 1 horizontal square = 0·2 ms. Note that in both panels A and B, the pulse amplitude remains unaffected by change in pulse width.*

for that particular type of pacemaker. However, it is equally important to be aware of the early results and problems related to the use of a newly introduced pacemaker.

In the Omnicor system the unipolar demand pacemaker's rate and output are controlled by an external, battery-powered programmer emitting electromagnetic pulses of 3 ms duration which open and close the magnetic reed switch within the pacemaker. Because programming pulses are recognised and counted by a binary counter in the pacer, invasive penetration of the patient is not required. The pacemaker rate can be adjusted from a low of 60 to a high of 100 pulses per min. Within this range the available rate selections are 60, 65, 70, 80, 90, and 100 pulses/min. There are 4 current output selections in the Omnicor system of 2·3 mA, 4 mA, 6 mA, and 9 mA (Fig 1). The respective dial settings on the programmer for the current output are labelled test (2·3 mA), low (4 mA), medium 6 mA), and high (9 mA). The programmer contains control switches for rate, stimulus current intensity, and the type of pacer being programmed.

In the Medtronic programmable 5961 system, the pacemaker is unipolar, with a titanium housing, and is capable of having the pulse duration (preset to 0·8 ms) changed noninvasively from 0·15 to 1·7 ms (Fig. 2). The potentiometer regulating pulse width is connected by a gear train to a small rotating magnet. This assembly is sealed in a metal cylinder in the centre of the pulse generator. The magnet in the pulse generator is driven by a rotating magnet of a hand-cranked external actuator. Coupling between the two magnets obtains at distances up to 3 in (7·5 cm). It is important to implant the pacemaker with the lettering facing upward, so that rotation of the external programmer results in pulse width changes indicated on the programmer. Pulse width changes are observed on the oscilloscope and it is essential that the electrocardiogram be simultaneously monitored to detect any unanticipated loss of pacing.

All pacemaker patients were systematically assessed in our special pacemaker follow-up clinic. The oscilloscopic analysis of the pacemaker pulse artefact was carried out using a Hewlett-Packard oscilloscope model 1201A. The pacemaker fixed rate was documented by the use of a customised Hewlett-Packard electronic counter, model 5307A, after application of a magnet to the pacemaker generator to induce a fixed rate. The chronic stimulation threshold in each patient was determined 6 to 8 weeks after permanent pacemaker implantation. The current output of the Omnicor pacemakers was programmed at two settings above the output level at which pacing ceased. For example, the setting was positioned at medium (6 mA) when no pacing resulted at the test setting (2·3 mA) (Fig 3). In the case when pacing was accomplished at test (2·3 mA), the setting was programmed at low (4 mA).

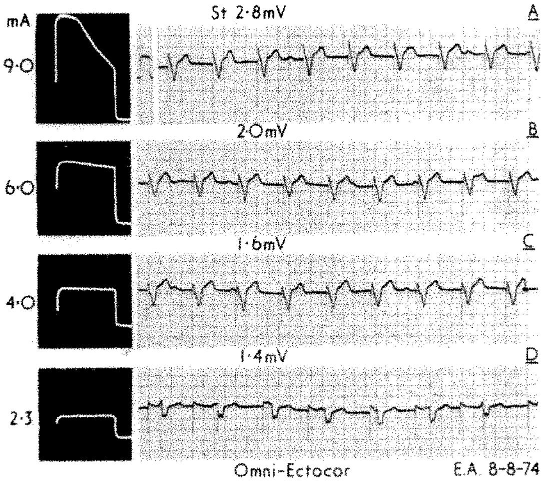

Fig. 3 *Representative pacemaker artefacts and corresponding electrocardiogram rhythm strips (lead II) showing the method for determining pacing threshold and thereby selecting chronic pacemaker current output using the Omnicor system. The electrocardiograph rhythm strips are shown on the right and the pacemaker artefact amplitude changes on the left. At the output setting of 9 mA (top row), there was 1:1 capture (A); the stimulus (St) artefact measured 2·8 mV. Decreasing the output to 6 and 4 mA, respectively (recordings B and C), showed decreasing oscilloscopic amplitude; the artefact amplitude decreased to 2 mV and 1·6 mV, respectively, and the electrocardiograph strips continued to show 1:1 capture. However, in the bottom strip D, decreasing pacemaker output to 2·3 mA resulted in loss of capture; pacemaker artefact amplitude declined to 1·4 mV. Note that in the bottom strip normal sensing is documented by the R-triggered pacemaker of all conducted QRS complexes occurring beyond the pacemaker refractory period.*

With the Medtronic system, the pulse width setting was programmed to 50 to 100 per cent above threshold width (Fig 4). The final pulse-width setting was determined by the pacemaker dependency of the patient. Thus, in our pacemaker clinic we have devised a system of grading how dependent a patient is on pacemakers by evaluating the intrinsic ventricular rate of the individual by terminating the pacemaker output pulses using chest-wall stimulation (Barold *et al.*, 1970). A patient with an intrinsic heart rate of 60 beats or more per minute is graded 1+; between 50 and 60 2+; 40 and 50 3+; 30 and 40 4+; and less than 30 beats

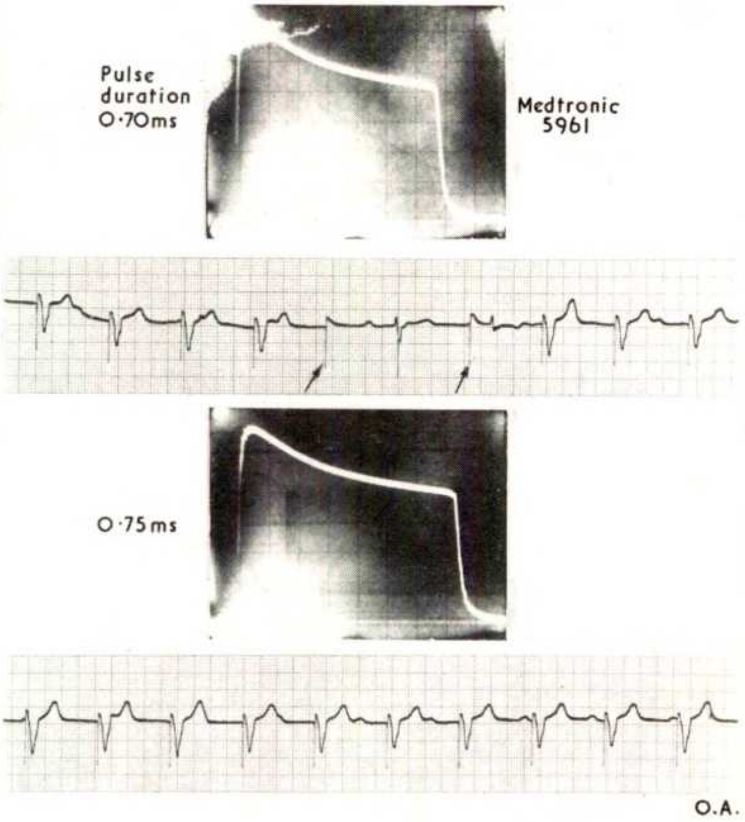

Fig. 4 *Representative pacemaker artefacts and corresponding electrocardiogram rhythm strips (lead II) showing the method for determining pulse width threshold and thereby selecting chronic pacemaker pulse width using the Medtronic system. The top strip shows pacemaker exit block (arrows) indicated by periods of noncapture of the pacemaker spike. The corresponding pulse width was 0·70 ms (top oscilloscopic tracing). Pulse width widening by the external pulse width controller to only 0·75 ms (bottom oscilloscopic tracing) resulted in constant 1:1 capture (bottom electrocardiogram strip). This patient had the highest pacing pulse width threshold of our Medtronic programmable series.*

per minute 5+. Patients with maximal dependency (4 and 5+) received at least a 100 per cent increase in pulse-width greater than threshold pulse width. Thereby patients at greatest risk of cardiac standstill received extra safeguard for uninterrupted pacing. Chronic stimulation thresholds were re-evaluated at least once every 6 months with both the Cordis and Medtronic units. When any significant fluctuation occurred from the initial threshold, appropriate current output (Cordis) or pulse-width (Medtronic) changes were made. All pacemakers showing impending battery exhaustion as determined by change in pacemaker fixed rate and/or alterations in the oscilloscopic amplitude or pulse-width (Parsonnet *et al.*, 1970) were replaced and the generator was sent to the manufacturer for analysis. All of our documented pacemaker failures were also proved by the manufacturer's analysis to have battery depletion.

Results

Of the 32 patients with Omnicor pacers, 4 died as a result of cardiac disease unrelated to pacemaker disorders or to the reason for pacer implantation before pacemaker battery depletion, and 3 who moved from the area were unavailable for follow-up assessment. Table 1 shows the current output and longevity of the demand Omnicor pacemakers in the remaining 25 patients. The current output and duration of pacemaker implant are presented on the horizontal axis. Pacemaker failure occurred in 5 of these patients because of battery exhaustion, with an average pacemaker life of 29·0 months (range 24 to 37 months). The mean current output during the functional life of 4 pacemakers which failed ranged from 4·0 to 5·2 mA (average 4·8 mA). The fifth patient, a 26-year-old woman (P.S.) with congenital heart block received her pacemaker in the first trimester of pregnancy. The current output was programmed to 9·0 and maintained at this setting until the onset of battery exhaustion at 27 months. Though this pacemaker never functioned as a low output unit, the average longevity of the other 4 units was 29·6 months. Therefore, the Omnicor

Table 1 *Omnicor longevity profile*

Case No.	*Time in months* 0 4 8 12 16 20 24 28 32 36 4
1	6 . . . . 4 X
2	6 . 9 . . . 4 . . . . →
3	6 . . . . →
4	6 . . . 9 . . . . →
5	6 . . . . 4 . . . . 6 X
6	6 . . . . →
7	6 . . . . →
8	6 . . 4 X
9	6 . 9 X
10	6 . . . . . . 9 . . . . →
11	6 . 9 . . . . 6 . . . . . . →
12	6 . . . . 4 . . . . →
13	6 . 4 X
14	6 . . . . 4 . . . . . . →
15	6 . . . . →
16	6 . . . . →
17	6 . 4 . . . . 9 . . . . →
18	6 . . . . . . 4 . . . . →
19	4 . . . . →
20	6 . . . 4 . . . . →
21	6 . . . . 4 . . . . →
22	6 . . . . . . →
23	6 . . . . →
24	6 . . . . →
25	6 . . . . →

Abbreviations: Numerical values of chronic current output (mA) used for pacing are indicated at the time of any change during follow-up. X = Pacemaker battery failure.

pacemaker longevity did not exceed that with non-programmable pacemakers in general (Furman and Escher, 1975). Furthermore, in 4 of 8 patients with non-programmable Cordis pacers in whom battery failure occurred, the range of longevity was 24 to 32 months (average 27·8 months), essentially the same as patients receiving programmable Cordis pacemakers. The relatively small number of the non-programmable Cordis pacemakers in our series reflects the almost exclusive use of the non-programmable Medtronic pacemakers at our institution before the introduction of programmable units. However, the longevity of the non-programmable Cordis units in our patients is not substantially different from that reported by others (Furman *et al.,* 1975).

Of the 24 patients receiving programmable Medtronic 5961 demand pacemakers (Table 2), 12 either died from cardiac disease which was not attributable to pacer dysfunction or to heart disease requiring pacemakers before battery exhaustion, or were unavailable for follow-up examination. Pacemaker failure occurred 19 months after implantation in one of the remaining 12 patients; manufacturer analysis revealed an open cap weld on one of the batteries as a cause of pacemaker failure. The other 11 programmable pacemakers are functioning now. Duration of operation has been 35 months in 1

Table 2 *Programmable Medtronic 5961 pacemaker longevity profile*

Case No.	*Time in months*										
	0	4	8	12	16	20	24	28	32	36	40
1	0·76	1·53			1·0				→		
2	0·8	0·3						→			
3	0·72	0·4						→			
4	0·8	0·3				0·34		→			
5	0·80						→				
6	0·76				0·2		→				
7	0·8	0·52					→				
8	0·9					→					
9	0·8					X					
10	0·8				→						
11	0·8			0·4 →							
12	0·8	→									

Abbreviations: Numerical values of chronic pulse width used for pacing are indicated temporally for individual patients at each change during follow-up.
X = Pacemaker battery failure.

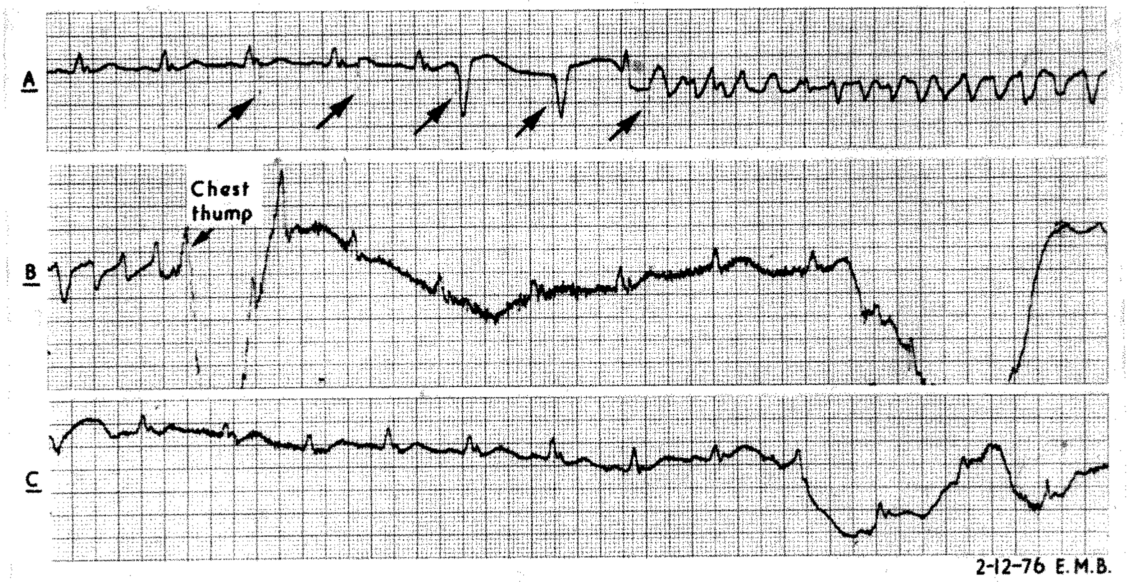

Fig. 5 *Ventricular flutter-fibrillation resulting from the R on T phenomenon with unipolar pacing in a patient with the Omnicor system who had sick sinus syndrome. In the normal fashion, the external magnet was placed over the normally functioning demand pacemaker for assessment of function. In the top strip of the electrocardiogram (lead II) (A), pacemaker spikes (first and second arrows) fall within the ST segments of the third and fourth QRS complexes. The fifth QRS complex is followed by two pacemaker-induced beats since the stimulus artefacts (third and fourth arrows) now fall beyond the refractory period of the conducted QRS complexes. The fifth pacemaker spike falls within the ST-T segment of a conducted QRS complex which resulted in the precipitation of ventricular-flutter fibrillation. In the second strip of the electrocardiogram (B), a chest thump (arrow) resulted in termination of the ventricular tachyarrhythmia with restoration of normal sinus rhythm (bottom electrogram strip C).*

patient, 28 months in 3, and approximately 24 months in another 2 patients (range 6 to 35 months; average 21·5 months). Though the exact longevity of the programmable Medtronic 5961 system is difficult to evaluate from the present information, it does appear that this pacemaker system may possess greater longevity than the programmable Omnicor units. Of 64 non-programmable Medtronic units, 14 failed during follow-up with an average of 32·6 months (range 23 to 48 months).

In a recent review of all documented instances of pacemaker-induced ventricular tachycardia or ventricular fibrillation in humans resulting from pacemaker stimulation during the vulnerable period of the preceding ventricular beat (R on T phenomenon), it was pointed out that all such episodes occurred with bipolar catheters and thereby anodal stimulation (Preston, 1973). However, in the course of this study we observed the first documented case of ventricular flutter fibrillation resulting from unipolar cathodal pacing in a patient with the Omnicor system who had sick sinus syndrome (Fig. 5). In the process of evaluating the patient's pacemaker function by applying a magnet over the pulse generator to convert from demand to fixed mode of operation, normally functioning pacemaker spikes were revealed. However, within a few seconds pacemaker spikes falling on the ST–T segment initiated a run of ventricular flutter-fibrillation (Fig. 5). Delivery of a timely chest thump resulted in the immediate reversion of the ventricular flutter-fibrillation to normal sinus rhythm.

Both types of programmable units have been claimed to withstand direct current countershock. However, in one instance in our series a patient with sick sinus syndrome with the demand Medtronic 5961 unit was cardioverted intraoperatively with direct current countershock from ventricular tachycardia to normal sinus rhythm. Immediately subsequent to countershock, the pacemaker lost its sensing ability. The patient was monitored for two days in the surgical intensive care unit and no episode of ventricular tachyarrhythmia resulting from fixed rate pacing was encountered. However, while awaiting surgical reimplantation of a new demand unit, the patient after disconnecting his

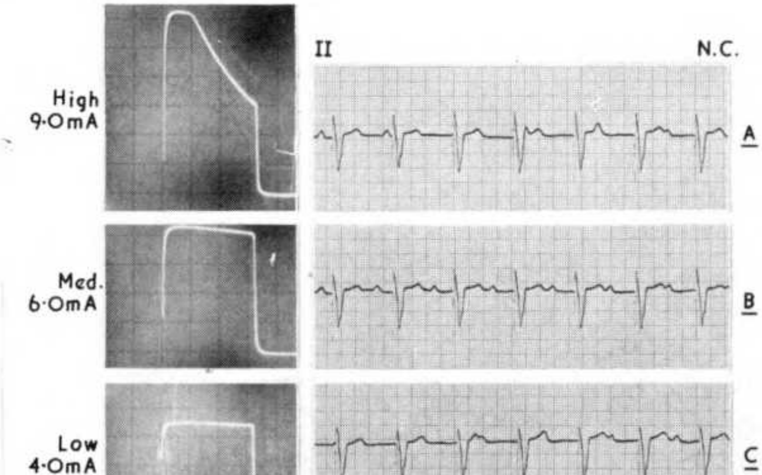

Fig. 6 *Illustration of the loss of pacing with the Omnicor system occurring at the test current setting. Simultaneous electrocardiogram strips A, B, and C show 1 :1 capture at the current amplitude settings of 9, 6, and 4 mA settings, respectively. Ventricular asystole occurred because of lack of capture (electrocardiogram strips D and E) at the test setting of 2·3 mA between the arrow on strip D and the arrow on strip E. 1 :1 capture immediately returned with the resetting of the current output at 6 mA following the arrow on strip E.*

monitoring leads, died suddenly during a short period of ambulation. Since no evidence of cardiovascular or pulmonary pathology was found at necropsy, the possibility of ventricular tachycardia resulting from fixed rate unipolar pacing was suspected. These two patients provide evidence that ventricular fibrillation can be induced by unipolar electrodes and, in addition, the latter patient indicates that demand pacemaker circuitry may be damaged by electroshock.

Because the threshold of cardiac stimulation is a linear function of the size of the cathode in contact with the endocardium (Furman *et al.*, 1975), the small surface area (12 mm^2) pacing electrode is commonly used. Introduction of programmable pacemakers was associated with an initial increase in the incidence of perforation of the right ventricle. This untoward complication was largely attributable to lack of familiarity of the physician to small surface area unipolar endocardial electrodes which tend to perforate the ventricular apex more readily as compared with larger bipolar electrodes. Within the first 5-month period of the present study, 6 patients undergoing programmable pacemaker insertion developed perforation of the right ventricle with the unipolar electrode catheter presenting as either sensing or pacing problems and requiring repositioning of intracardiac electrode. However, with careful intraoperative monitoring of the intracardiac electrogram from the unipolar pacemaker electrode catheter (Vera *et al.*, 1976), the incidence of perforation with implantation of programmable pacemakers has been virtually eliminated.

Caution is emphasised in evaluating pacing thresholds both with the Omnicor and Medtronic systems. Fig. 6 shows loss of pacing at the test current setting associated with ventricular asystole. Likewise, Fig 7 shows loss of capture and ventricular asystole associated with narrowing of the pulse width using the Medtronic programmer.

Since their introduction in November 1972 the Omnicor pacemakers revealed defects resulting in premature battery depletion because of unforeseen manufacturing defects observed in late 1973 and

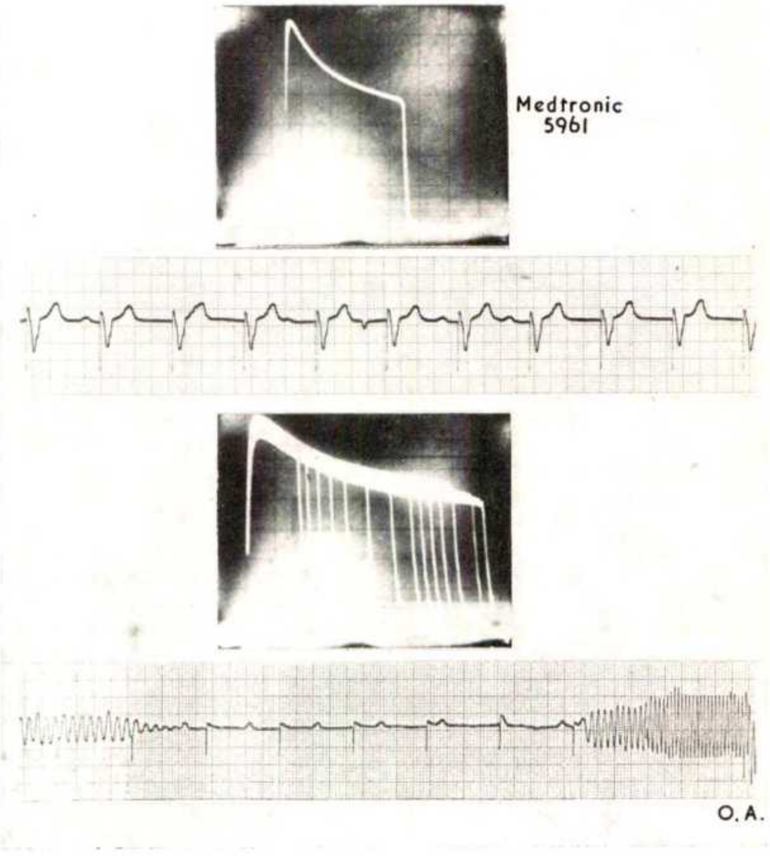

Fig. 7 *Illustration of the problem of loss of pacing and ventricular asystole with the Medtronic system occurring during narrowing of pulse width. The top strip on the electrocardiogram shows 1 :1 capture with a pulse width of 0·8 ms (top oscilloscopic tracing). The middle portion of the bottom strip of the electrocardiogram shows ventricular asystole because of lack of pacemaker capture with the narrowed pulse width (bottom oscilloscopic tracing). Capture was immediately regained with widening of the pulse width. The undulations at the beginning and end of the bottom strip of the electrocardiogram indicate artefact induced by rotation of the handcrank programmer.*

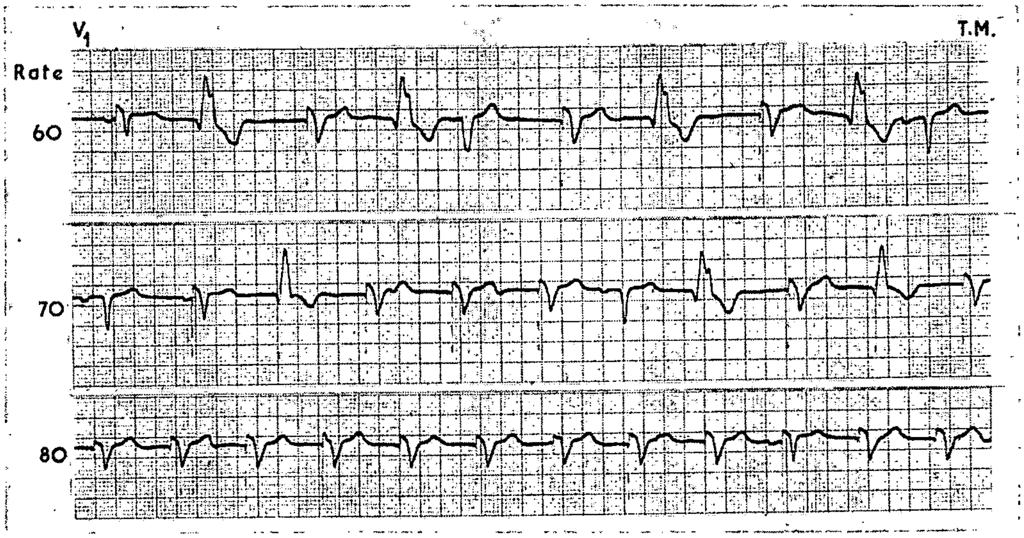

Fig. 8 *Programmable pacemaker overdrive suppression of multiple premature ventricular contractions using the Omnicor system. This patient with trifascicular disease had spontaneous ectopy at the pacemaker rate of 60/min despite oral antiarrhythmic therapy (top strip of electrocardiogram). In the middle strip at the pacemaker rate of 70/min fewer ectopic beats occurred. Complete overdrive suppression was achieved by increasing the pacemaker rate to 80/min (bottom strip of the electrocardiogram).*

early 1974. These instances of premature failure occurred in certain substandard lots within 5 to 14 months of implant and resulted from inclusion or intrusion of moisture causing malfunction of the sealed hybrid circuits. This problem has since been corrected. Occasional transient periods of non-sensing were encountered in the early months of Omnicor use. However, pacemaker replacement has not been necessary because of the brief and diminishing frequency of this defect and no patient complications have been encountered.

Discussion

Since 1960 with the onset of the era of permanently implantable cardiac pacemakers, it has been realised that two important prerequisites for an ideal pacemaker are: (1) atrial synchronised ventricular pacing and (2) long lasting power source. The former feature re-establishes atrioventricular conduction in complete heart block. However, because of several problems, especially the unavailability of a stable atrial electrode, routine use of a transvenous atrial synchronous ventricular pacemaker is not yet possible.

Concerning the second principal characteristic, the mercury-zinc cell has been the mainstay power source since the original pacemakers. With improvements in pacemaker technology and engineering, component failure is rarely encountered at the present time. Therefore, the majority of pacemaker replacements are undertaken because of battery exhaustion. Despite improvements in battery design and the reduction of current leakage, pacemaker life by 1974 averaged only 32 months (Furman *et al.*, 1975). Thus, frequent replacements of the pulse generator continue to be necessary.

The two alternatives available to the pacemaker industry relative to the problem of pacemaker longevity have been the development of new power sources and more efficient use of energy available in the mercury-zinc cell. With the introduction of programmable units in late 1972, it was predicted that battery life would be considerably extended by judicious matching of the pacemaker energy output to patient need. The functional battery life of the Cordis Omnicor pacemaker system was projected to be 2 years, with an output setting of 9 mA, nearly 3 years at an output setting of 6 mA, 3·5 years with 4 mA, and 4·5 years with an output setting of 2·3 mA. From these data the reported expected life of the Omnicor pacers has been estimated to be between 3 and 7 years.

The Medtronic pulse width controllable system (Model 5961) has a projected longevity of nearly 5 years with a pulse width setting of 0·3 ms. The pulse width of the programmable Medtronic pacemakers automatically increases with depletion of the first mercury cell in the five-battery stack compensating for voltage reduction to maintain capture.

There are two independent indicators of battery depletion, pulse width increase and decrease in pacing rate. The current drain at narrower pulse width settings is much less than at wider pulse durations. Decreasing the pulse width of the Medtronic 5961 model from 1·0 ms to 0·3 ms has been shown to reduce the current drain from 19 microamperes per pulse to 10 microamperes, a saving of nearly 50 per cent in energy. Therefore, the reported theoretical life of the same pacemaker has been estimated to be 3·5 years (pulse width 1·0 ms) to nearly 5 years (pulse width 0·3 ms). Postulations of longevity are calculated theoretical battery life and do not take into account pacemaker malfunction caused by random component failure. These projections by the manufacturers were based on knowledge of current drains delineated above using the Medtronic 5816 endocardial lead with an uninhibited pacing rate of 72/min. In arriving at these predicted life spans, only 27 months of actual pacemaker testing had been carried out *in vitro*.

From the above theoretical considerations of anticipated extension of lifetime of pacemakers by programmable units, it is clear that actual evaluation of such systems in patients is of the utmost importance. No published reports before the present study have been available concerning the actual lifespan of current programmable pacemakers in clinical trials. The data presented herein of programmable pacemaker longevity in 36 patients who were followed for an average of 23 months indicate that the pacemaker life span postulated by the manufacturers appears to be considerably overestimated. Thus, 6 of the 37 patients experienced pacemaker failure (5 Cordis and 1 Medtronic) because of battery exhaustion at an average of only 27·3 months after implantation. Furthermore, these early results for Omnicor pacemakers were not significantly better than the control longevity of the standard Cordis and Medtronic demand pacemakers which failed an average of 31·5 months after insertion.

Although the added manipulations which attend programmable pacemakers do not appear to increase pacemaker longevity substantially at this time, there are several important reasons for retaining the programmable function (albeit with a longer lived power source). First, the ability to change heart rate is useful in patients in whom optimal cardiac output is achieved at relatively higher heart rates. Secondly, in patients with sinus bradycardia or in second degree atrioventricular heart block a slower programmed rate allows atrial transport of ventricular filling. Thirdly, the programmable systems with ability to pace at higher rates provide overdrive suppression of ventricular tachyarrhythmias (Fig. 8). Fourthly, serial evaluation of the patient's chronic stimulation threshold provides early diagnosis and appropriate management of the occasional patient with high pacing threshold (exit block). Finally, a very slow pacemaker rate allows evaluation of the patient's intrinsic rhythm QRS complexes and ST-T segments.

From the above observations it appears evident that the available Omnicor system using mercury-zinc batteries probably will not provide the hoped for extension of pacemaker longevity of greater than 5 years. The alternative power source of lithium iodide appears to be a most promising approach to the problem of longer pacemaker life and deserves thorough clinical evaluation which is under way at our institution.

References

Barold, S. S., Pupillo, G. A., Gaidula, J. J., and Linhart, J. W. (1970). Chest wall stimulation in evaluation of patients with implanted ventricular-inhibited demand pacemakers. *British Heart Journal*, **32**, 783–789.

Chardack, W. M., Baken, E. E., Bolduc, L., Giori, F. A., and Gage, A. A. (1971). Magnetically actuated pulse width control for implanted pacemakers: Its significance for follow-up of patients and the reduction of current drain. *Annales de Cardiologie et d'Angéiologie*, **20**, 345–355.

Furman, S., and Escher, D. J. W. (1975). Transtelephone pacemaker monitoring: five years later. *Annals of Thoracic Surgery*, **20**, 326–336.

Furman, S., Garvey, J., and Hurzeler, P. (1975). Pulse duration variation and electrode size as factors in pacemaker longevity. *Journal of Thoracic and Cardiovascular Surgery*, **69**, 382–389.

Morse, D., Samuel, A., Fernandez, J., Lemole, G., and Parsonnet, V. (1975). Preliminary experience with the use of a programmable pacemaker. *Chest*, **67**, 544–548.

Parsonnet, V., Meyers, G. H., Gilbert, L., and Zucker, I. R. (1970). Prediction of impending pacemaker failure in a pacemaker clinic. *American Journal of Cardiology*, **25**, 311–319.

Preston, T. A. (1973). Anodal stimulation as a cause of pacemaker induced ventricular fibrillation. *American Heart Journal*, **86**, 366–372.

Vera, Z., Mason, D. T., Awan, N. A., Janzen, D., McMillin, D., Mokhtar, S., Detje, R. L., and Ikeda, R. (1976). Cardiac perforation by endocardial pacemaker electrodes: Clinical evaluation with special reference to role of intracardiac electrography. *Clinical Research*, **24**, 244A.

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Type and frequency of cardiac defects in embryofetal alcohol syndrome

Report of 16 cases

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Within a period of 3 years, 56 infants and children with embryofetal alcohol syndrome have been detected and examined for heart defects. All children were from mothers who had been addicted to alcohol even during pregnancy and they showed a typical pattern of malformations, as described by Lemoine et al. *(1968) and Jones* et al. *(1973).*

In 16 cases cardiovascular malformations were confirmed by heart catheterisation or pathological examination. The overall incidence of heart defects in this syndrome was 29 per cent. The incidence rises to nearly 50 per cent in the more severe types of this syndrome. Atrial septal defects were found to be the most common heart defect (10 out of 16 cases); ventricular septal defects and other variable malformations occurred less frequently.

The high incidence of heart defects indicates that alcoholism during pregnancy has to be considered as a serious and preventable cause of congenital heart disease.

Previous clinical studies on the embryofetal alcohol syndrome resulting from severe maternal alcoholism in pregnancy indicate that alcohol is a teratogenic agent. Alcoholism during pregnancy may produce multiple malformations including heart defects in the offspring. We owe it to Lemoine *et al.* (1968) in Nantes, France, and Jones *et al.* (1973, 1974) in the USA for recognising a typical pattern of malformations in this syndrome, which is characterised by the following basic features: prenatal and postnatal growth retardation; retardation of mental, psychomotor, and motor development; craniofacial dysplasia, particularly microcephaly, short palpebral fissures, ptosis of the upper lids, epicanthic folds, upturned nostrils ('nez court en trompettes'), and mandibular hypoplasia (Fig. 1A and B). Other malformations are frequently found, such as heart defects, abnormalities of the limbs or genitals, dermatoglyphs, etc. The malformations vary in individuals in number and in severity.

The prevalence and types of cardiac defects in the embryofetal alcohol syndrome are still matters of controversy. On the basis of our first reports of 8 confirmed cases, atrial septal defect was thought to be the most frequent abnormality (Löser *et al.*, 1975, 1976). On the basis of other reports, however, the most frequent defect seemed to be ventricular septal defect. Little information is available concerning the frequency of cardiovascular malformations in this syndrome. Since an increase in the number of alcohol-consuming women of child-bearing age is to be expected in all industrial countries, the question of cardiovascular malformations in the embryofetal alcohol syndrome is important both prophylactically and therapeutically.

Subjects and methods

Following our first reports of heart diseases in embryofetal alcohol syndrome (Löser *et al.*, 1975), we were able to detect in our clinic a total of 16 infants and children with congenital heart disease in 56 cases with the syndrome (Bierich *et al.*, 1976; Majewski *et al.*, 1976). The observation spanned a 3-year period. In all these 56 cases the heart was examined clinically and chest radiographs and electrocardiograms were obtained. If reasonably certain indications of cardiac defect were present, heart catheterisation and angiocardiography were performed.

All patients were children of mothers who had

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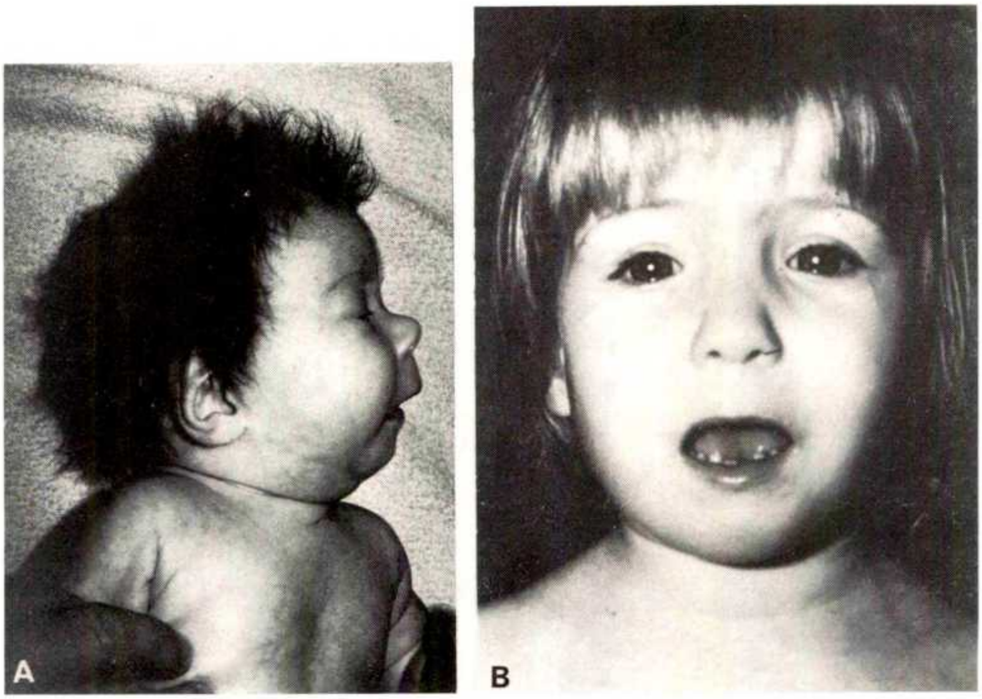

Fig. 1 (A) and (B) *Typical facies of children with embryofetal alcohol syndrome. The narrow palpebral fissures, the upturned nostrils, the hypoplasia of the mandible, and the vermilion border of the upper lip are noteworthy.*

drunk excessive amounts of alcohol for several years, even during pregnancy. An estimate of the alcohol intake was obtained from case histories and expressed as grams of ethanol per day. In addition, data concerning alcohol-related diseases, duration of pregnancy, birthweights, and gestational ages were collected. Children of mothers who were only occasional drinkers were not included. The minimal alcohol consumption admitted by the mothers ranged from 75 to 350 g/day. As is typical with alcoholics, the actual amounts must be assumed to be higher and, therefore, could not be established precisely. Additional drug intake was noted in as far as it was admitted.

Because of the broad spectrum of symptoms in this syndrome, the 56 cases of embryofetal alcohol syndrome have been divided into three groups according to the occurrence and severity of mental, neurological, and physical abnormalities (Majewski *et al.*, 1976).

Grade 1 (20 cases): oligosymptomatic cases with only slight expression of morphological features. Except for reduced body weight and microcephaly these children showed no manifestations typical of the syndrome. Abnormal development in utero was in some cases less important than postnatal growth retardation which usually persisted into later childhood. Motor development was moderately delayed in most cases. Mental age did not seem to differ from that of normal subjects.

Grade 2 (19 cases): moderately affected cases. The craniofacial dysmorphism was not striking, but sufficiently pronounced to be apparent to those with some experience in its recognition. In this group there were no neurological manifestations, except for hyperexcitability and hypotonia of the muscles. Mental and physical development were moderately delayed.

Grade 3 (17 cases): severely affected cases with all or nearly all the typical abnormalities. All cases showed pronounced craniofacial changes: microcephaly, epicanthic folds, ptosis, upturned nostrils, thin vermilion border of the upper lip, and mandibular hypoplasia. Physical, motor, and mental development were seriously delayed in all cases.

Results

The historical data and catheterisation results in our 16 cases are summarised in Tables 1 and 2. They comprise 7 girls and 9 boys between the ages of 1 month and 6 years. Except for cases 13 and 14 the birthweights were below 2500 g, and the data in Table 1 show that these children were premature and/or small for dates at birth. The overall incidence of heart defects in embryofetal alcohol syndrome was 29 per cent. There was a tendency for the more severely affected to have a higher incidence of heart defects: thus cardiovascular malformations occurred in 1 of 20 cases with grade 1 changes, 5 of 19 cases with grade 2 changes, and 10 of 17 cases with grade 3 changes. If the mildly affected cases of grade 1 are excluded, heart defects were present in 15 of 36 children (42%).

Atrial septal defects were found in 10 cases. In one of these distinct displacement of the heart to the left and hypoplastic left pulmonary arteries were shown. In one case of atrial septal defect, catheterisation was not justified during life because of respiratory problems and internal hydrocephalus. The heart is shown in Fig. 2. At histological examination of both ventricles no abnormal structure of the muscle fibres or other signs of cardiomyopathy were found. In all cases additional left-sided defects were

Table 1 *Birthweights, gestational ages, and history of maternal alcohol abuse*

Case No.	*Birthweight*	*Gestational age (wk)*	*Duration of abuse before birth (y)*	*Minimum amounts of alcohol in pregnancy (g/day)*	*B = beer W = wine S = spirit*	*Further indications of maternal alcoholism*
1	1600	39	5	?	S	Withdrawal treatment; fatty liver (histol.)
2	1970	40	4	?	S	Diffuse fatty liver (histol.); barmaid; tremulous states
3	1970	35	6	190	S	—
4	1790	32	6	150	B	Delirium tremens; generalised convulsions (children of same mother)
5	2410	36	4	300	B	
6	2080	41	14	125	B, S, W	Tremulous states in 4th month of gestation; fatty liver
7	2110	32	10	100	W, B	Withdrawal treatment: delirium tremens
8	2280	41	7	190	W, S, B	—
9	2000	35	11	350	S	Several suicidal attempts
10	2290	40	2	75	S, B	2 withdrawal treatments without success
11	2000	40	7	250	B, S	Mother died from hepatic coma 1 y after delivery
12	1380	32	2–3	100	S, B	Barmaid, divorce because of drinking
13	3300	40	11	300	W	2 withdrawal treatments; delirium tremens; alcoh. damage of liver; epilepsy for 11 y; drugs in pregnancy: 3 × 0·1 g phenytoin/day
14	2950	40	4	250	B, S	Delirium tremens (2); drunk during delivery
15	2420	36	3	125	S, B, W	Withdrawal treatment; damage of liver; drugs in pregn.: up to 10 tabl. Thomapyrin°/day (=2·5 g aspirin +2·0 g phenacetin)
16	1810	36	5	240	B, S	Withdrawal treatment; diffuse fatty liver (histol.); tremulous states

Table 2 *Embryofetal alcohol syndrome: results of catheterisation*

Case No.	*Sex*	*Age**		*Diagnosis*	*Shunt*	*Qp/Qs*	*Pulmonary hypertension*	*Notes*
		y	*mth*					
1	M		7	ASD II	L-R	1,3	0	
2	F		2	ASD II	L-R	1,7	0	Died; mild supravalv. pulm. stenosis
3	M		2	ASD II	L-R	2,3	0	
4	M	1	6	ASD II	L-R	2,1	0	
5	F		7	ASD II	L-R	1,1	0	Displacement of the heart to the left; hypoplast. left pulm. art.
6	F		3	ASD II	L-R	2,4	0	
7	F		9	ASD II	L-R	—	—	Died; heart section; int. hydroceph.
8	F		8	ASD II	L-R	1,9	0	
9	M	6	9	ASD II	L-R	2,2	0	
10	M	3	4	Aplasia right PA	0	1,0	0	Collateral arteries to right lung
11	F	4	3	Mild IHSS	0	1,0	0	
12	M	4	5	VSD	L-R	1,3	++	Right aortic arch
13	F	2	4	VSD	L-R	1,8	0	
14	M	1	1	AV—canal	L-R	—	+	
15	M		1	Infund. PS, VSD	R-L	0,5	0	Died; hypoxic spells
16	M	1	6	ASD II	L-R	1,7	0	

*At time of catheterisation; + = mild, ++ = moderate; Qp/Qs = pulmonary to systemic flow ratio; PS = pulmonary stenosis.

excluded by angiocardiography. Electrocardiograms showed no evidence of left axis deviation.

An isolated ventricular septal defect was found in 2 cases, one of which had a right-sided aortic arch and pulmonary hypertension (Fig. 3).

In other isolated cases, variable defects were found. In one case aplasia of the right pulmonary artery was established (Fig. 4), which was also confirmed by lung perfusion scintigraphy. In one case a mild obstruction of the left ventricular outflow tract was found. One case of atrioventricular canal, and one case of infundibular pulmonary stenosis and ventricular septal defect with pronounced cyanosis were also shown.

Two infants died from extracardiac causes (cases 2 and 7), at the ages of 5 and 9 months. One infant died in the course of hypoxic spells and respiratory troubles at the age of 4 months (case 15).

The catheterisation and electrocardiographic data gave no reliable signs of cardiomyopathy in any subject.

Discussion

The frequent appearance of cardiac defects in the embryofetal alcohol syndrome can now be regarded as established. No exact data regarding the frequency of cardiac defects in children from alcoholic mothers are available. There are several reasons for this:

(1) The degree of severity and the expression of

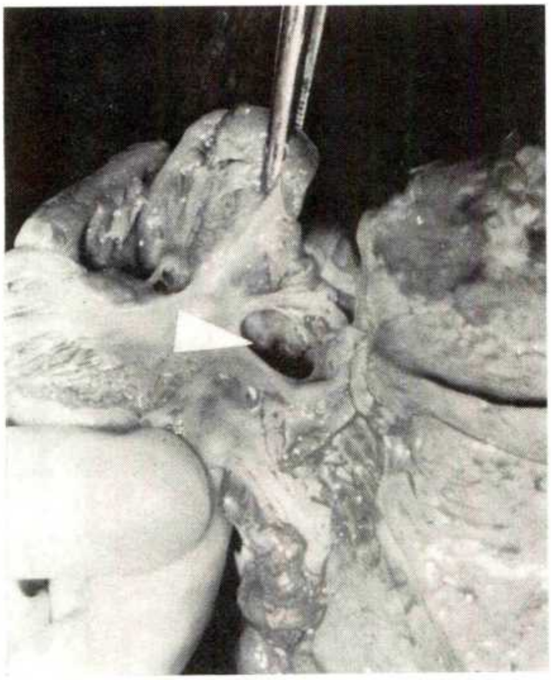

Fig. 2 *Case 7. Portion of the heart. The arrow indicates a large atrial septal defect (secundum type).*

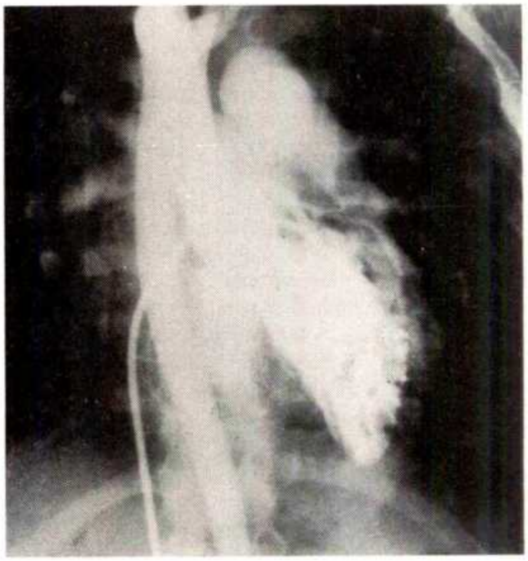

Fig. 3 *Case 12. Angiocardiogram after injection into the left ventricle. Filling of the right ventricle and the pulmonary artery. Right-sided aortic arch.*

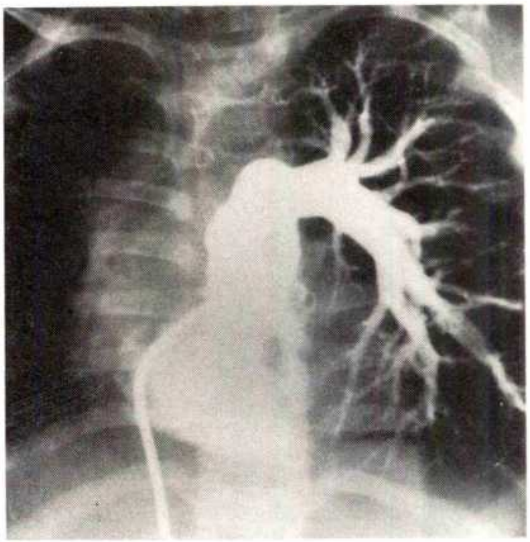

Fig. 4 *Case 10. Angiocardiogram showing absence of the right pulmonary artery.*

manifestations varied in our observations and also in other published studies. They range from mild (*'formes frustes'*) to severe cases (grade 1–3, Majewski *et al.*, 1976). This depends more on the drinking pattern and the individual tolerance than on the absolute quantity of alcohol consumed (Majewski *et al.*, 1976). The question remains whether infants with only a slight expression of symptoms should be included in the embryofetal alcohol syndrome.

(2) In many currently reported cases of embryofetal alcohol syndrome, the diagnosis of heart defect is based only on clinical findings (see Table 3). It has been suggested that heart defects can be expected in nearly 50 per cent of all cases (Jones *et al.*, 1973; Löser *et al.*, 1975). This percentage, however, seems to be too high if the cases of mild degree are included. But if only the cases of grades 2 and 3 are considered the percentage rises to 42 per cent, and in severe degrees to more than 50 per cent (9 of 16). A definitive statement concerning the frequency of heart defects will be possible only when more extensive material is available and investigated.

The influence of concurrent drug intake did not appear to be significant in our study.

In contrast to the currently available reports, particularly that of Jones *et al.* (1973), the most frequent malformation of the heart is atrial septal defect and not ventricular septal defect. An atrial septal defect was diagnosed in 10 out of 16 cases, an isolated ventricular septal defect in 2 cases. According to the reported clinical observations (Table 3), ventricular septal defect was often suspected, but the typical sharp harsh murmur was seldom described. Noonan (1976) recently presented a paper on 3 cases with embryofetal alcohol syndrome and heart defects. Two of these had tetralogy of Fallot.

Based on experimental studies, particularly the chick embryo and mouse embryo (Sandor, 1968; Chernoff, 1976), it has been confirmed that ethylalcohol affects embryonic development, produces a high mortality rate, and alters early growth as well as differentiation and morphogenesis in cardiac development. Sandor and Elias (1968) described a lack of circulation in beating embryonic hearts after

Table 3 *Summary of published cases of embryofetal alcohol syndrome with cardiac defects*

Author	*Case No.*	*Sex*	*Age*		*Heart defect*	*Heart catheter.*	*Notes*
			y	*m*			
Jones *et al.* (1973)	1	F	1		VSD suspected	ϕ	Spontan. closure
	2	F		11	ASD	+	Heart failure
	3	F	4	3	VSD suspected	?	Spontan. closure suspected
	4	F	3	9	PDA suspected	?	—
	8	M	2	6	VSD suspected	ϕ	Spontan. closure suspected
Jones and Smith (1973)	1	M	Newborn		VSD suspected	ϕ	—
	2	F	Newborn		VSD	ϕ	Died; pathol. examination
	3	F		7	VSD suspected	ϕ	—
Palmer *et al.* (1974)	2	F	1	9	VSD suspected	ϕ	Twins
	3	F	1	9	?	ϕ	(systolic murmur)
Saule (1974)	1	F	Newborn		VSD suspected	ϕ	—
Manzke and Grosse (1975)	4	M	6		Defect suspected	ϕ	—
	7	M		9	Mitr. stenosis	+	Infrahepat. stenosis IVC
Reinhold *et al.* (1975)	2	F		4	VSD suspected	ϕ	—
Löser *et al.* (1975)	1	M		7	ASD	+	
	2	F		2	ASD	+	Died, 5th mth
	3	M		2	ASD	+	
	4	M	1	6	ASD	+	
	5	F		7	ASD	+	
	10	M	3	4	Aplasia r. PA	+	
	11	F	4	3	Mild IHSS	+	
	12	M	4	5	VSD, r. ao. arch	+	
Mulvihill *et al.* (1976)	2	M		1	PAST suspected	ϕ	
Noonan (1976)	1	?	4		T/F	+	
	2	?	6		T/F	+	
	3	?	17		VSD, PDA	+	

Abbreviations: ao., aortic; ASD, atrial septal defect; IHSS, idiopathic hypertrophic subaortic stenosis; IVC, inferior vena cava; PA, pulmonary artery; PAST, pulmonary artery stenosis; PDA, persistent ductus arteriosus; T/F, tetralogy of Fallot; VSD, ventricular septal defect. ϕ, catheterisation not performed.

exposure to alcohol. Chernoff (1976) noted a higher rate of heart defects on the eighteenth day of gestation in developing mice during exposure to alcohol. The type of defects in the heart and great vessels were, however, not elaborated.

The cardiovascular malformations produced by thalidomide during pregnancy represent a comparable embryotoxic effect on the developing heart (Khera, 1976). Congenital heart disease was found in approximately 19 per cent of the children affected by thalidomide embropathy (Keck *et al.*, 1971). As with thalidomide embryopathy, the critical period for toxic injury to the developing heart is assumed to be between the fourth and sixth week of gestation. It is expected that the spectrum of cardiovascular defects in embryofetal alcohol syndrome is more extensive than has been known up to now.

Previous investigations indicate that it is the ethanol itself and not its metabolites, such as acetaldehyde, that is responsible for the direct damage to the embryo, since alcohol is able to cross the placental barrier readily. Moreover, it is known that alcohol metabolism is deficient in chronic alcoholics and also in the human fetal liver. The concentration of alcohol dehydrogenase in the human fetal liver is extremely low (Pikkarainen and Räihä, 1967) and ethanol clearance is reduced (Seppälä *et al.*, 1971), which enhances the toxic influence.

It is surprising that widespread alcoholism during pregnancy has not been recognised earlier as a cause of congenital heart disease, since many women as well as men have been addicted to alcohol for generations.

We thank Prof. Dr. med. Jüngst, Univ. — Kinderklinik Mainz, West Germany, for permission to include case 14.

References

Bierich, J R., Majewski, F., Michaelis, R., and Tillner, I. (1976). Uber das embryo-fetale Alkohol-Syndrom. *European Journal of Pediatrics*, **121**, 155–177.

Chernoff, G. F. (1976). A mouse model of the fetal alcohol syndrome. *Teratology*, **11**, 14A.

Jones, K. L., and Smith, D. W. (1973). Recognition of the fetal alcohol syndrome in early infancy. *Lancet*, **2**, 999–1001.

Jones, K. L., Smith, D. W., Streissguth, A. P., and Myrianthopoulos, N. C. (1974). Outcome in offspring of chronic alcoholic women. *Lancet*, **1**, 1076–1078.

Jones, K. L., Smith, D. W., Ulleland, C. N., and Streissguth, A. P. (1973). Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet*, **1**, 1267–1271.

Keck, E. W., Roloff, D., and Markworth, P. (1971). Kardiovaskuläre Befunde bei Kindern mit Thalidomid-Dysmelie-Syndrom. *Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung*, **37**, 364–370.

Khera, K. S. (1976). Fetal cardiovascular and other defects induced by thalidomide in cats. *Teratology*, **11**, 65–72.

Lemoine, P. H., Harousseau, H., Borteyru, J. P., and Menuet, J.-C. (1968). Les enfants de parents alcooliques. Anomalies observées apropos de 127 cas. *Ouest-Médical*, **25**, 477–482.

Löser, H., Majewski, F., Apitz, J., and Bierich, J. R. (1975). Kardiovaskuläre Fehlbildungen bei fetalem Alkoholsyndrom. *Zeitschrift für Kardiologie*, Suppl. 2, 91.

Löser, H., Majewski, F., Apitz, J., and Bierich, J. R. (1976). Kardiovaskuläre Fehlbildungen bei embryofetalem Alkohol-Syndrom. *Klinische Padiatrie*, **188**, 233–240.

Majewski, F., Bierich, J. R., Löser, H., Michaelis, R., Leiber, B., and Bettecken, F. (1976). Zur Klinik und Pathogenese der Alkohol-Embryopathie. Bericht über 68 Fälle. *Münchener medizinische Wochenschrift*, **118**, 1635–1642.

Manzke, H., and Grosse, F. R. (1975). Inkomplettes und komplettes 'fetales Alkoholsyndrom' bei drei Kindern einer Trinkerin. *Medizinische Welt*, **26**, 709–712.

Mulvihill, J. J., Klimas, J. T., Stokes, D. C., and Risemberg, H. M. (1976). Fetal alcohol syndrome: seven new cases *American Journal of Obstetrics and Gynecology*, **125**, 937–941.

Noonan, J. A. (1976). Congenital heart disease in the fetal alcohol syndrome. *American Journal of Cardiology*, **37**, 160.

Palmer, R. H., Ouellette, E. M., Warner, L., and Leichtman, S. R. (1974). Congenital malformations in offspring of a chronic alcoholic mother. *Pediatrics*, **53**, 490–494.

Pikkarainen, P., and Räihä, N. C. R. (1967). Development of alcohol dehydrogenase activity in the human liver. *Pediatric Research*, **1**, 165–168.

Reinhold, L., Hütteroth, H., and Schulte-Wissermann (1975). Das fetale Alkohol-Syndrom. Fallbericht über 2 Geschwister. *Münchener medizinische Wochenschrift*, **117**, 1731–1734.

Sandor, S. (1968). The influence of aethyl alcohol on the development of the chick embryo. II. *Revue Roumaine Embryologie et de Cytologie. Série d'embryologie*, **5**, 167–171.

Sandor, S., and Elias, S. (1968). The influence of aethyl-alcohol on the development of the chick embryo. *Revue Roumaine Embryologie et de Cytologie. Série d'embryologie*, **5**, 51–76.

Saule, H. (1974). Fetales Alkohol-Syndrom. Ein Fallbericht. *Klinische Padiatrie*, **186**, 452–455.

Seppälä, M., Räihä, N. C. R., and Tamminen, V. (1971). Ethanol elimination in a mother and her premature twins. *Lancet*, **1**, 1188–1189.

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Sudden death after operative repair of tetralogy of Fallot

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The clinical and necropsy findings in 3 patients with tetralogy of Fallot who died suddenly after corrective operation are presented. Early postoperative electrocardiograms of 2 patients showed coexistent right bundle-branch block and left anterior hemiblock; one of these developed complete atrioventricular block and required a pacemaker. In the third patient, postoperative electrocardiograms showed anterior myocardial infarction. At necropsy, there was gross and histological evidence of myocardial infarction in each patient. After operation, extensive myocardial fibrosis and the development of right bundle-branch block and left anterior hemiblock are possible factors causing cardiac arrhythmias and sudden death.

Sudden death has been reported after corrective surgery of tetralogy of Fallot and is related to the development of conduction disturbances in the divisions of His bundle. We have seen 3 such patients with tetralogy of Fallot; each died more than 6 months after complete repair of the anomaly and in each a healed myocardial infarction was found at necropsy. The preoperative electrocardiogram in each case was typical of tetralogy of Fallot. After operation, the electrocardiograms of one patient showed the pattern of anterior myocardial infarction. The electrocardiograms of the other 2 patients showed left axis deviation and complete right bundle-branch block; while this pattern has been observed in postoperative electrocardiograms in association with the subsequent development of complete heart block and sudden death, we wish to describe the finding of myocardial infarction in such patients.

Case reports

CASE 1

This 8-year-old boy was diagnosed as tetralogy of Fallot at the age of 4 years, and a right Blalock-Taussig shunt was performed. At the age of 7 years, at operation for complete correction of his cardiac anomaly, infundibular muscle was resected through a longitudinal ventriculotomy, the ventricular septal defect was closed by a 'teflon' patch, and a pulmonary valvotomy was performed. Though he required a tracheostomy in the immediate postoperative period, he made good progress after this. The postoperative electrocardiogram (Fig. 1) showed abnormal Q waves in praecordial leads V4R to V5, suggestive of extensive anterior myocardial infarction. The patient was taking digitalis at the time of discharge, but this was later discontinued. Subsequently, the patient attended school and was able to play without dyspnoea or cyanosis. He still had a grade 2/6 systolic ejection murmur at the upper left sternal border. He died suddenly, 9 months after operation, while playing at home.

Necropsy findings

The external surface of the heart showed healed fibrous pericarditis. The interior of the right and left atria was normal. The right ventricle was slightly dilated. An anomalous muscle bundle ran from the anterior wall of the ventricle to the septal band but did not appear obstructive. There was conspicuous endocardial sclerosis of the right ventricular outflow tract and the septal wall of the right ventricle. The anterior wall of the right ventricle was thinned and scarred along the ventriculotomy incision. No residual ventricular septal defect or outflow obstruction was present. The pulmonary valve was tricuspid, each cusp being thickened.

In the anterior wall of the left ventricle and the ventricular septum, there was an oval healed transmural myocardial infarction, measuring 6·0 × 4·0

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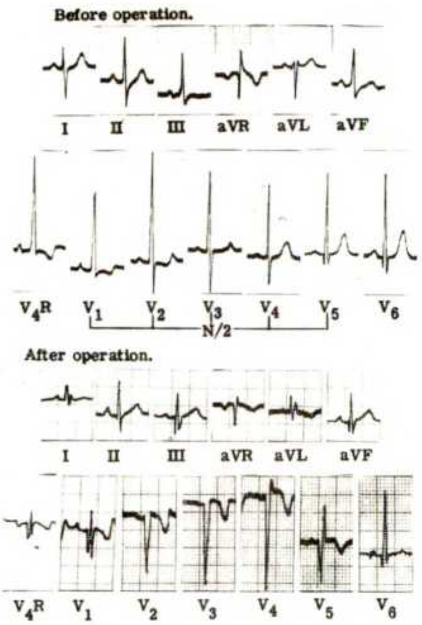

Fig. 1 *Case 1. Preoperative electrocardiogram shows QRS axis +120° and right ventricular hypertrophy. N/2 = half standardisation. Postoperative electrocardiogram shows deep Q waves and inverted T waves in praecordial leads, indicating anterior myocardial infarction.*

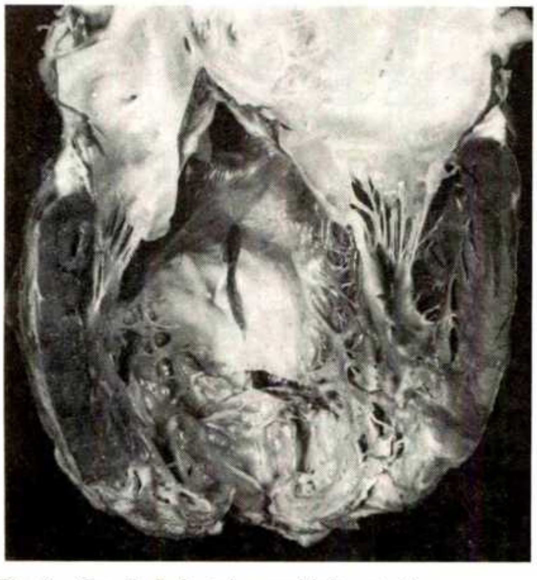

Fig. 2 *Case 1. Left atrium and left ventricle. Thickened white endocardium over ventricular septum. Apex of ventricle thinned.*

cm (Fig. 2). The ventricular septum was thinned and the endocardium covering the infarcted area was thickened. In addition, the apical region of the left ventricle showed myocardial scarring. Both sides of the patch covering the ventricular septal defect were covered with thick, fibrous tissue. The origin and distribution of the coronary arteries were normal. The right branch of the left anterior descending coronary artery was involved in the fibrous tissue and sutured in the region of the right ventriculotomy.

Microscopical examination of the ventricular septum and the anterior wall of the left ventricle showed extensive fibrosis with replacement of the myocardium by bands of fibrous tissue and collagen. There was proliferative endocardial fibrosis, especially on the right ventricular surface of the ventricular septum.

CASE 2

In this 14-year-old boy the diagnosis of tetralogy of Fallot was made in infancy, and a left Blalock-Taussig shunt was performed at the age of 3 years. At the age of 13 years, he had a corrective operation. A vertical right ventriculotomy was performed, since an unusually prominent branch of the right coronary artery lay across the right ventricular infundibulum. The infundibular obstruction was resected and the ventricular septal defect was closed with a 'teflon' patch. A pulmonary valvotomy was performed, and a constricting band immediately below the pulmonary annulus was also excised.

At the end of the operation, the patient appeared to be in nodal rhythm, but sinus rhythm returned spontaneously. Complete atrioventricular dissociation was noted in the first 48 hours after the operation, but again sinus rhythm returned spontaneously. The postoperative electrocardiogram showed complete right bundle-branch block. The mean frontal plane QRS axis of the unblocked portion of the QRS complex was −90° (Fig. 3).

The patient remained well for 9 months, but was then found to be in complete heart block and a pacemaker was implanted. Five months later, the pacemaker wire was broken during an automobile accident. After repair of the wire, the patient was admitted repeatedly for infection of the pacemaker pocket and pacemaker malfunction. A new set of myocardial electrodes and pacemaker were implanted. Seven days later, death occurred from ventricular fibrillation.

Necropsy findings

The heart was much enlarged and showed evidence of healed, fibrous pericarditis. The right atrium and

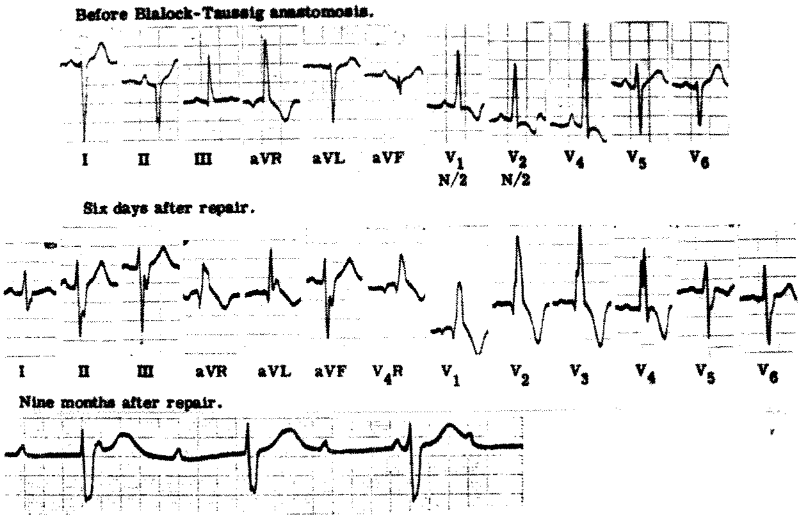

Fig. 3 *Case 2. Preoperative electrocardiogram shows right axis deviation and right ventricular hypertrophy. N/2 = half standardisation. Electrocardiogram after operation shows right bundle-branch block, with frontal QRS axis of unblocked portion −90°. The third record shows complete heart block.*

right ventricle were dilated. The septal leaflet of the tricuspid valve showed thickened, fused chordinae tendineae. In the inflow region the wall thickness of the right ventricle was 1·2 mm, while proximal to the infundibular region this was 5 mm. The endocardium of the right ventricle showed generalised thickening, particularly in the region of the closed ventricular septal defect and the outflow tract. There was no residual outflow obstruction and no residual ventricular septal defect. The pulmonary valve was bicuspid and dysplastic. A circumferential fibrous ring in the pulmonary trunk created supravalvar stenosis.

The left atrium and the mitral valve were normal. The left ventricle showed hypertrophied walls and endocardial thickening, the latter being greater in the subaortic region. The origin and distribution of the coronary arteries were normal. The aortic arch was right sided with mirror-image branching.

Microscopical examination of the outflow position of the right ventricle showed extensive transmural myocardial infarction with endocardial and pericardial fibrosis (Fig. 4). Occasional foreign body giant cells were seen around the suture material. A moderate amount of fibrosis was present in the ventricular septum. Except for pericarditis and some epicarditis, the myocardium of the left ventricle was normal. Sections along the course of the bundle of His and the atrioventricular node showed fibrous strands intermingling with these structures, and in some areas densely surrounding them.

CASE 3

This 6-year-old boy was first seen at the age of 3½ months because of severe cyanosis. A diagnosis of tetralogy of Fallot was made and a Brock pulmonary valvotomy was performed. At the age of 4 years, cardiac catheterisation and right ventriculogram showed tetralogy of Fallot with a long area of infundibular narrowing. Complete correction was performed when he was 6 years of age. The outflow tract was enlarged by infundibular resection and a 'teflon' outflow patch. The ventricular septal defect was closed with considerable difficulty with another 'teflon' patch. During resection of infundibular muscle, the ventricular septum was inadvertently incised in the region of the crista supraventricularis.

The electrocardiogram after the operation showed complete right bundle-branch block (Fig. 5). The frontal plane QRS axis of the unblocked portion of the QRS complex was −105°.

The patient remained in congestive cardiac failure after the operation and required repeated hospital admissions. Physical findings were consistent with a residual ventricular septal defect and angiocardiographic studies confirmed its presence. The patient died after cardiac arrest, while in the hospital for management of congestive cardiac failure, 10 months after the corrective operation.

Necropsy findings

The external surface of the heart showed healed pericarditis. The right atrium was slightly dilated

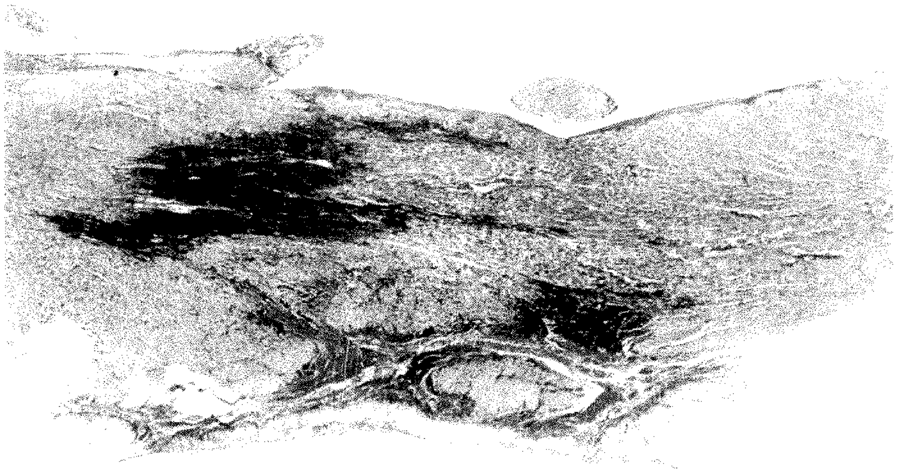

Fig. 4 *Case 2. Extensive fibrosis of right ventricular myocardium. (×4·2.)*

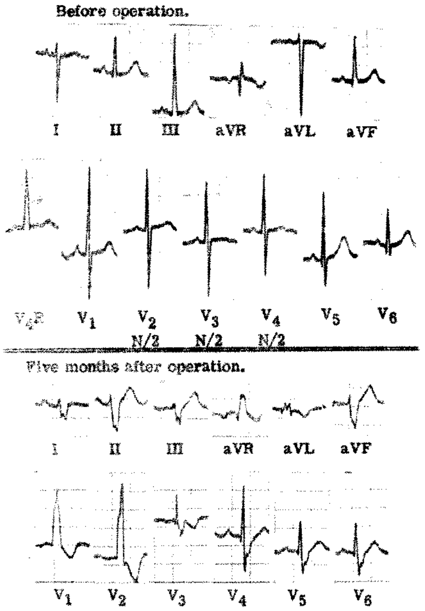

Fig. 5 *Case 3. Preoperative electrocardiogram shows QRS axis +120° and right ventricular hypertrophy (N/2 = half standardisation). Postoperative electrocardiogram shows complete right bundle-branch block and left axis deviation.*

and the left atrium was normal. The anterior and septal walls of the right ventricle showed extensive scarring that extended into the outflow tract (Fig. 6a). There was no residual right ventricular outflow obstruction. The ventricular septal defect had been incompletely closed and measured 12×4 mm. The anterior portion of the ventricular septum was very thin, from about 2 cm below the pulmonary valve to the apex, and there was an 8×5 mm interventricular communication in this part of the septum. The pulmonary valve was bicuspid and thickened.

The left ventricular cavity was dilated, and there was endocardial thickening involving the septal wall and the region of the apex (Fig. 6b). The endocardial thickening extended to the subaortic region. The anterior interventricular communication in the muscular septum was surrounded by extensive scarring and thinning of the septum. In addition, there was scarring of the left ventricular wall in the region of the apex. The origin and distribution of the coronary arteries were normal.

Microscopical examination of the ventricular septum showed extensive fibrosis in the region of the infarcted area. Some of the intramyocardial branches of the coronary arteries showed proliferative intimal fibrosis. There was mild scarring of the free wall of the left ventricle.

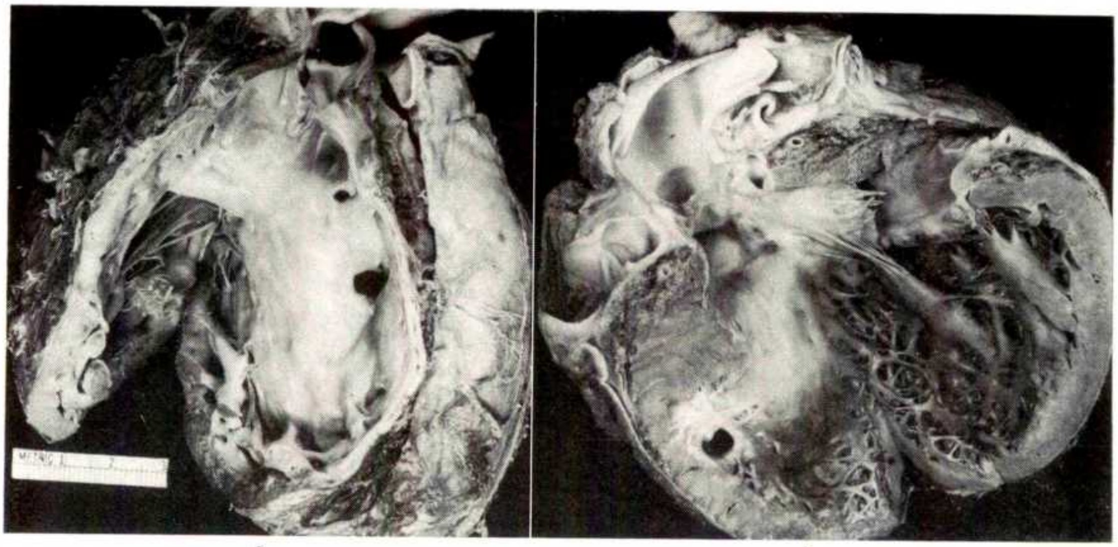

Fig. 6 *Case 3.* (a) *Right ventricle with extensive thickening of endocardium and circular defect in midportion of muscular ventricular septum.* (b) *Left ventricle with muscular ventricular septal defect.*

Discussion

Ischaemic necrosis of the myocardium and interruption of the conduction bundles have been reported after right ventriculotomy and closure of ventricular septal defect (Korns *et al.*, 1969; Kulbertus *et al.*, 1969; Gelband *et al.*, 1971). The myocardial necrosis has been thought to be related to surgical division of the coronary arteries which show an anomalous distribution over the outflow area of the right ventricle. Our study indicated, however, that it is not necessary for distribution of the branches of the coronary arteries to be abnormal for myocardial infarction to occur after operation in patients with tetralogy of Fallot.

Extensive fibrosis of the ventricular septum and anterior wall of the right ventricle was seen in all our patients, each of whom showed a normal coronary arterial distribution. These patients died unexpectedly, though each showed an electrocardiographic abnormality: this was coexistent left axis deviation and complete right bundle-branch block in cases 2 and 3, with the later development of complete heart block in case 2, and an anterior myocardial infarct pattern in case 1.

Grant (1956) first pointed out that a superior orientation of the QRS complex may be seen in patients with coronary arterial disease and anterolateral myocardial infarction. Later, the presence of a similar QRS pattern was described in patients with extensive myocardial fibrosis but without coronary arterial disease (Banta *et al.*, 1964). Left axis deviation has thus been related to fibrosis in the left ventricle. More recently, however, left axis deviation has been thought to represent interruption of the anterior fasciculus of the left bundle-branch.

A QRS axis of approximately –60° with Q waves in leads I and aVL has been described as left anterior hemiblock (Aravindakshan *et al.*, 1970; Rosenbaum *et al.*, 1970b).

The development of left axis deviation after operation has been described in patients with ventricular septal defect as well as in those with tetralogy of Fallot (Kulbertus *et al.*, 1969; Rosenbaum *et al.*, 1970a; Wolff *et al.*, 1972). Frequently these patients, as in our two, have in addition complete right bundle-branch block, yielding a pattern of bifascicular block. Such patients appear vulnerable to the development of complete heart block resulting from disturbance in conduction of the remaining portion of the left posterior fasciculus, as perhaps developed in one of our patients.

There are few histological studies of the conduction system in these postoperative patients to indicate the histopathology of this condition. We studied the conducting system of one of our patients (case 2) and found fibrous strands in the atrioventricular node and bundle of His and surrounding tissue; there was, however, no actual interruption of the conducting system.

Death was sudden in our 3 patients and ventricular arrhythmias are presumed to have been the cause. In the 2 patients with a combination of right bundle-branch block and left anterior hemiblock, death could be explained by progression to complete heart block and related arrhythmias, including cardiac standstill. In the other patient (case 1), with electrocardiographic evidence of myocardial infarction, myocardial damage with resulting fibrosis may have been responsible for arrhythmias, as in patients with coronary disease dying suddenly after myocardial infarction without conduction disturbances. It is not possible to determine from our study whether the arrhythmias and consequent sudden death were directly related to injury of the conduction tissue, resulting in right bundle-branch block and left anterior hemiblock in two cases, or to myocardial damage (infarction), or to both.

Finally, we recommend close electrocardiographic control in the follow-up of patients who develop right bundle-branch block and left anterior hemiblock, with or without atrioventricular conduction disturbances, or a myocardial infarction pattern, after complete correction.

References

Aravindakshan, V., Elizari, M. V., and Rosenbaum, M. B. (1970). Right bundle-branch block and left anterior fascicular block (left anterior hemiblock) following tricuspid valve replacement. *Circulation,* **42,** 895–902.

Banta, H. D., Greenfield, J. C., Jr., and Estes, E. H., Jr. (1964). Left axis deviation. *American Journal of Cardiology,* **14,** 330–338.

Gelband, H., Waldo, A. L., Kaiser, G. A., Bowman, F. O., Jr., Malm, J. R., and Hoffman, B. F. (1971). Etiology of right bundle-branch block in patients undergoing total correction of tetralogy of Fallot. *Circulation,* **44,** 1022–1033.

Grant, R. P. (1956). Left axis deviation. An electrocardiographic-pathologic correlation study. *Circulation,* **14,** 233–249.

Korns, M. E., Schwartz, C. J., Edwards, J. E., and Lillehei, C. W. (1969). Pathologic sequelae and complications of ventriculotomy. I. With special reference to the myocardium. *Archives of Pathology,* **88,** 269–283.

Kulbertus, H. E., Coyne, J. J., and Hallidie-Smith, K. A. (1969). Conduction disturbances before and after surgical closure of ventricular septal defect. *American Heart Journal,* **77,** 123–131.

Rosenbaum, M. B., Corrado, G., Oliveri, R., Castellanos, A., Jr., and Elizari, M. V. (1970a). Right bundle branch block with left anterior hemiblock surgically induced in tetralogy of Fallot. Relation to the mechanism of electrocardiographic changes in endocardial cushion defects. *American Journal of Cardiology,* **26,** 12–19.

Rosenbaum, M. B., Elizari, M. V., and Lazzari, J. O. (1970b). *The Hemiblocks.* Tampa Tracings, Olsdmar, Florida.

Wolff, G. S., Rowland, T. W., and Ellison, R. C. (1972). Surgically induced right bundle-branch block with left anterior hemiblock. An ominous sign in postoperative tetralogy of Fallot. *Circulation,* **46,** 587–594.

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Bradycardia-dependent peri-infarction block

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A case is reported in which electrocardiographic signs appeared during the acute phase of myocardial infarction, which we have interpreted as indicating bradycardia-dependent peri-infarction block.

Bradycardia-dependent intraventricular block of the bundle-branch type (paradoxical bundle-branch block) is a recognised electrocardiographic finding (Massumi, 1968; Sarachek, 1970). Similarly, focal (Rosenbaum *et al.*, 1968) or intramyocardial (Hecht and Kossmann, 1973) block, during the acute phase of myocardial infarction (peri-infarction block), unrelated to rate, has been previously documented (First *et al.*, 1950; Shadaksharappa *et al.*, 1968). Tachycardia-related focal block has also been reported (Gambetta and Childers, 1973). However, to our knowledge a bradycardia-dependent peri-infarction block has not yet been reported, and it constitutes the subject of this paper.

Case report

A 60-year-old male patient was first seen in June 1970 with typical anteroseptal myocardial infarction. He made an uneventful recovery but remained in clinical class II, with physical signs of ventricular asynergy. For over a year the ST segment was still displaced (Fig. 1A) in leads I, aVL, and V2 to V6, though he was still in sinus rhythm at 70 bpm, with a PR of 0·16 s, QRS of 0·09 s, and a frontal plane AQRS of 90°. In October 1971 he had an episode of weakness and diaphoresis, without chest pain, lasting 2 hours. Three days later he presented with pulmonary oedema and the electrocardiogram showed sinus tachycardia at 102 bpm, PR 0·21 s, left atrial enlargement, widening of the QRS to 0·11 s, and no changes in either the frontal plane AQRS or the initial vectors (Fig. 1B). However, the late vectors were changed in III, aVF and aVL, producing a W-shaped complex in the last lead. Left ventricular failure persisted and 6 days after the episode of weakness the electrocardiogram showed an atrial rate of 120 bpm and a ventricular rate of 60 bpm, with a 2:1 atrioventricular block and a bizarre QRS configuration (Fig. 1C). The latter showed a slowing of the ventricular depolarisation process after the first 0·05 to 0·06 s, lasting 0·08 to 0·09 s, and resulting in a wide QRS of 0·18 s. The erythrocyte sedimentation rate and white blood cells were raised on the same day but no increase in enzyme level was noted. On the following day both the 2:1 atrioventricular block and the peri-infarction block disappeared (Fig. 1 D).

An electrocardiogram obtained on the afternoon of the same day (14 October 1971) showed a sinus rate of 109 bpm (PP interval of 0·55 s), a 3:2 atrioventricular block of the Wenckebach type (4:3 in V6), and a ventricular response with the following characteristics (Fig. 2): alternating cycle lengths of 1·02 and 0·63 s; the long pauses being terminated by wide QRS of the type described above, and short pauses terminated by normal duration QRS. It can be seen from this tracing that the early vectors are identical for both types of complexes, mainly in right praecordial leads, while there is an obvious delay in activation after those early vectors.

Discussion

The clinical picture, laboratory findings, and electrocardiographic abnormalities are suggestive of a new infarct in the lateral wall of the left ventricle, probably in an area near the previous infarction. On the sixth day a transient second degree atrioventricular block associated with intraventricular conduction delay was noted. This conduction defect shows a different morphology than the usual defect found in either total or partial bundle-branch block, but retains the characteristic features of peri-infarction block (First *et al.*, 1950). This case also presents several clinical similarities with the cases reported by Shadaksharappa *et al.* (1968): onset in the first week of a myocardial infarction, being transient and more frequent during a second infarction.

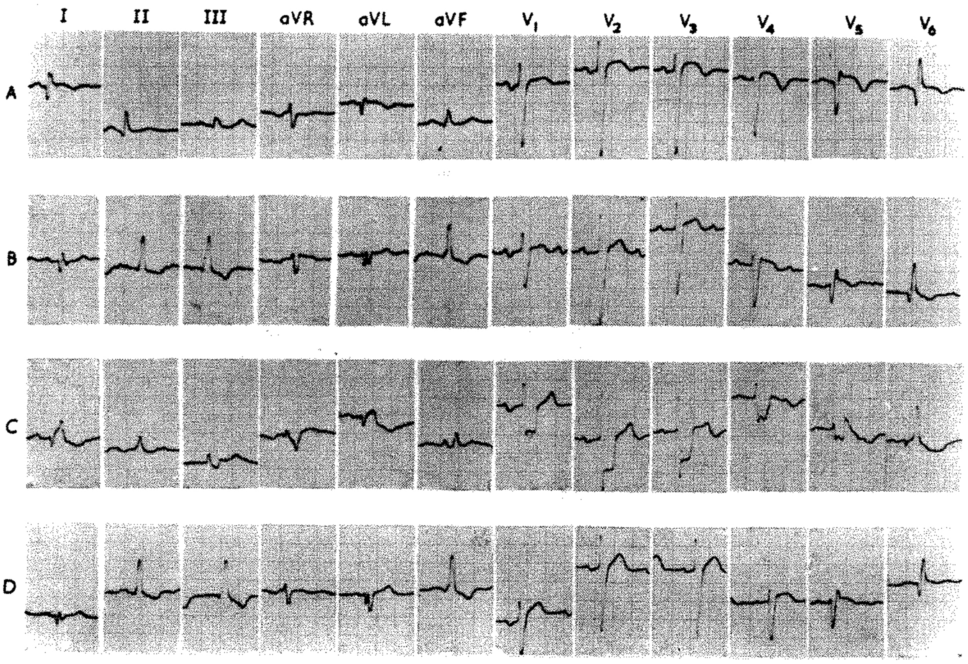

Fig. 1 *(A) Electrocardiogram a year after the first infarction. (B) Acute phase of second infarction before appearance of 2 : 1 atrioventricular block. (C) Acute phase of second infarction: appearance of 2 : 1 atrioventricular block and peri-infarction block. (D) Acute phase of the second infarction after atrioventricular block.*

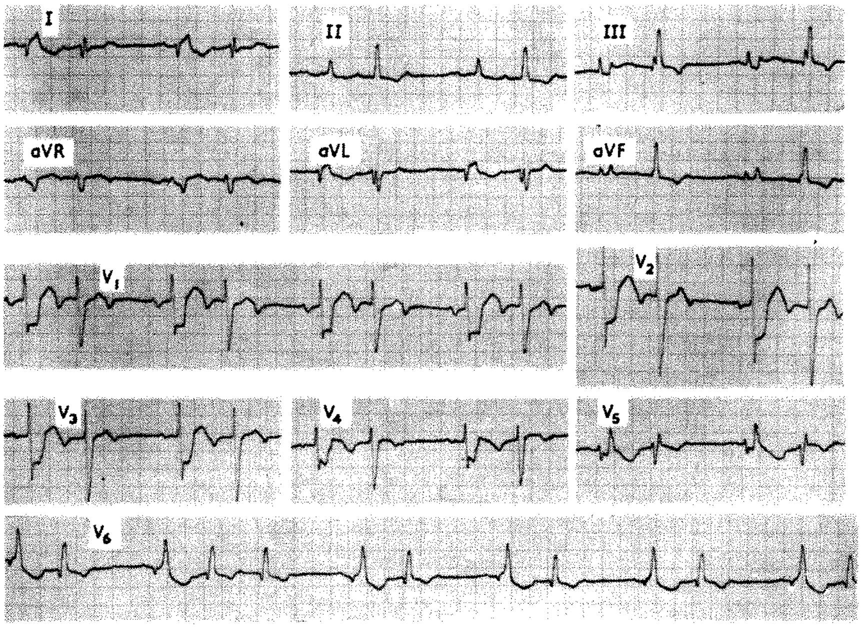

Fig. 2 *Bradycardia-dependent peri-infarction block recorded during 3 : 2 atrioventricular block.*

A change from 2:1 to 3:2 atrioventricular block revealed the most interesting finding: the intraventricular conduction delay became intermittent, appearing always after the long pauses and disappearing after the short ones, best seen during the 4:3 block recorded in V6. This rate-dependent peri-infarction block behaves like the paradoxical bundle-branch block which sometimes accompanies a variable atrioventricular block during the course of a myocardial infarction (Puech and Grolleau, 1972).

It might be speculated whether the block is located in the distal Purkinje system or in the myocardial fibres. The former will most probably alter the initial vector forces, like the fascicular or the focal septal block described by Gambetta and Childers (1973). Its occurrence in the latter part of the QRS (0·05 s after the onset) and its duration (0·08 to 0·09 s) suggest a conduction delay within the myocardial fibres affected by the ischaemic insult. Its appearance only during the prolonged RR intervals explains the name of paradoxical or bradycardia-dependent peri-infarction block.

The early work of Singer *et al.* (1967) was followed by numerous reports of slow rate-related arrhythmias, i.e. paradoxical bundle-branch block (Massumi, 1968; Sarachek, 1970), aberrant late nodal beats (Sarachek, 1970), normalisation of WPW syndrome with slow rhythms (Massumi and Vera, 1971), paroxysmal atrioventricular blocks (Coumel *et al.*, 1971; Rosenbaum *et al.*, 1973), and the underlying mechanism of other types of arrhythmias like intermittent parasystole (Cohen *et al.*, 1973), and intermittent bigeminy (Levy *et al.*, 1975).

According to these reports, several factors might increase the slope of phase 4 of the Purkinje system and, consequently, a late stimulus could find the diastolic potential less negative, producing an action potential of diminished amplitude with decreased dV/dT of phase 0, resulting in conduction disturbance. A similar situation is produced when a premature stimulus falls on the early part of phase 3, before complete repolarisation is reached. Both disturbances are voltage dependent (Singer *et al.*, 1967; Singer and TenEick, 1971), and the conduction delays associated with rapid or slow rhythms have been called phase-3 and phase-4 blocks (Rosenbaum *et al.*, 1973), though some authors prefer to call them tachycardia- or bradycardia-dependent blocks (El-Sherif, 1972).

It appears that the critical factor is an increase in extracellular potassium following the cell necrosis during the course of a myocardial infarction (Harris, 1966; Sutton and Davies, 1968; Lazzara and Sherlag, 1972). It is difficult to explain a tachycardia-dependent block, in a disease state, only on the basis of voltage changes of phase 3; other factors, such as the time relation and the sodium pump, a decrease of the resting potential, or cell membrane responsiveness, are probably involved (Fisch *et al.*, 1973; El-Sherif *et al.*, 1974; Neuss *et al.*, 1974). In bradycardia-dependent block, besides the slope of phase 4, other factors such as hypopolarisation, increase in threshold potential, and alterations of cell membrane responsiveness might play a role (Singer *et al.*, 1967; El-Sherif *et al.*, 1974; Neuss *et al.*, 1974; Rosenbaum *et al.*, 1974; Kretz *et al.*, 1975).

Under normal conditions myocardial cells do not have automaticity, but during an ischaemic insult they may suffer electrophysiological changes, such as spontaneous diastolic depolarisation during phase 4 (Solberg *et al.*, 1972), which, if associated with other factors, will cause the block; on the other hand, if we accept these changes at the myocardial cell level, the case reported here would be an instance of pacemaker activity of these cells.

The combination of a variable atrioventricular block and intramyocardial block make it possible to speculate on a common aetiological factor, such as the increase in extracellular potassium.

Lastly, why is this a rare phenomenon? If we consider the frequency of peri-infarction block (39%—Shadaksharappa *et al.*, 1968) and also of atrioventricular nodal block during infarction (3%—Stock and Macken, 1968), at least 1 per cent of the infarction cases would meet the necessary conditions of heart rate and cell necrosis for its appearance. The fact that paradoxical block is less frequently seen as peri-infarction block than as bundle-branch block, makes us think that the conditions necessary for the occurrence of the first are more difficult to meet. In our case all these rare circumstances were present: old infarction, acute infarction in a nearby area, variable atrioventricular block, and patient survival.

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References

Cohen, H., Langendorf, R., and Pick, A. (1973). Intermittent parasystole—Mechanism of protection. *Circulation*, **48**, 761–774.

Coumel, P., Fabiato, A., Waynberger, M., Motte, G., Slama, R., and Bouvrain, Y. (1971). Bradycardia-dependent atrioventricular block. Report of two cases of AV block elicited by premature beats. *Journal of Electrocardiology*, **4**, 168–177.

El-Sherif, N. (1972). Tachycardia-dependent versus bradycardia-dependent intermittent bundle-branch block. *British Heart Journal*, **34**, 167–176.

El-Sherif, N., Scherlag, B. J., Lazzara, R., and Samet, Ph. (1974). Pathophysiology of tachycardia- and bradycardia-dependent block in the canine proximal His-Purkinje system after acute myocardial ischemia. *American Journal of Cardiology,* **33,** 529–540.

First, S. R., Bayley, R. H., and Bedford, D. R. (1950). Peri-infarction block; Electrocardiographic abnormality occasionally resembling bundle-branch block and local ventricular block of other types. *Circulation,* **2,** 31–36.

Fisch, Ch., Zipes, D. P., and McHenry, P. L. (1973). Rate dependent aberrancy. *Circulation,* **48,** 714–724.

Gambetta, M., and Childers, R W. (1973). Rate-dependent right precordial Q-waves: 'Septal focal block'. *American Journal of Cardiology,* **32,** 196–201.

Harris, A. S. (1966). Potassium and experimental coronary occlusion. *American Heart Journal,* **71,** 797–802.

Hecht, H. H., and Kossmann, C. E. (1973). Atrioventricular and intraventricular conduction. Revised nomenclature and concepts. *American Journal of Cardiology,* **31,** 232–244.

Kretz, A., Da Ruos, H. O., and Leguizamon Palumbo, J. R. (1975). Delay and block of cardiac impulse caused by enhanced phase-4 depolarization in the His-Purkinje system. *British Heart Journal,* **37,** 136–149.

Lazzara, R., and Scherlag, B. J. (1972). Washout of arrhythmogenic substance liberated after coronary occlusion. *Circulation,* **45–46,** Suppl. II, 116.

Levy, M. N., Adler, D. S., and Levy, J. R. (1975). Three variants of concealed bigeminy. *Circulation,* **51,** 646–655.

Massumi, R. A. (1968). Bradycardia-dependent bundle-branch block. A critique and proposed criteria. *Circulation,* **38,** 1066–1073.

Massumi, R. A., and Vera, Z. (1971). Patterns and mechanisms of QRS normalization in patients with Wolff-Parkinson-White syndrome. *American Journal of Cardiology,* **28,** 541–554.

Neuss, H., Thormann, J., and Schlepper, M. (1974). Electrophysiological findings in frequency-dependent left bundle-branch block. *British Heart Journal,* **36,** 888–898.

Puech, P., and Grolleau, R. (1972). *L'Activité du Faisceau de His Normale et Pathologique.* Editions Sandoz, Paris.

Rosenbaum, M. B., Elizari, M. V., Chiale, P., Levi, R. J., Nau, G. J., Halpern, M. S., Lázzari, J. O., and Novakovsky, A. (1974). Relationships between increased automaticity and depressed conduction in the main intraventricular conducting fascicles of the human and canine heart. *Circulation,* **49,** 818–828.

Rosenbaum, M. B., Elizari, M. V., and Lázzari, J. O. (1968). *Los Hemibloqueos.* Paidos, Buenos Aires.

Rosenbaum, M. B., Elizari, M. V., Lázzari, J. O., Halpern, M. S., Nau, G. J., and Levi, R. I. (1973). The mechanism of intermittent bundle-branch block: relationship to prolonged recovery, hypopolarization and spontaneous diastolic depolarization. *Chest,* **63,** 666–677.

Sarachek, N. S. (1970). Bradycardia-dependent bundle branch block: Relation to supernormal conduction and phase 4 depolarization. *American Journal of Cardiology,* **25,** 727–729.

Shadaksharappa, K. S., Kalbfleisch, J. M., Conrad, L. L., and Sarkar, N. K. (1968). Recognition and significance of intraventricular block due to myocardial infarction (peri-infarction block). *Circulation,* **37,** 20–26.

Singer, D. H., Lazzara, R., and Hoffman, B. F. (1967). Interrelationships between automaticity and conduction in Purkinje fibers. *Circulation Research,* **21,** 537–558.

Singer, D. H., and TenEick, R. E. (1971). Aberrancy: electrophysiologic aspects. *American Journal of Cardiology,* **28,** 381–401.

Solberg, L., TenEick, R., and Singer, D. (1972). Electrophysiological basis of arrhythmia in infarcted ventricle. *Circulation,* **45–46,** Suppl II, 116.

Stock, R. J., and Macken, D. L. (1968). Observations on heart block during continuous electrocardiographic monitoring in myocardial infarction. *Circulation,* **38,** 993–1005.

Sutton, R., and Davies, M. (1968). The conduction system in acute myocardial infarction complicated by heart block. *Circulation,* **38,** 987–992.

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Myocardial ultrastructural changes in Kugelberg-Welander syndrome[1]

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Electron microscopical study of a biopsied specimen of myocardium from a patient with the Kugelberg-Welander syndrome revealed myocardial degeneration, including preferential loss of myosin filaments and abnormalities in the Z bands. Leptomeric fibrils were also observed in the cardiac muscle cell; there does not appear to be a previous report of the finding of such fibrils in human myocardium.

It has been reported that the heart can be involved in the Kugelberg-Welander (K-W) syndrome (Matsumoto *et al.*, 1971; Sterz *et al.*, 1971; Sugimura *et al.*, 1973), a spinal muscular atrophy described by Wohlfart *et al.* (1955), and Kugelberg and Welander (1956). Recently, we reported 2 cases of this syndrome with cardiomyopathy and reviewed the published reports (Tanaka *et al.*, 1976).

To our knowledge, there has not been any report of the fine structural changes of the myocardium in the K-W syndrome. In this communication, we describe the results of electron microscopical examination of myocardium from a patient with the K-W syndrome.

Case history

A 20-year-old man was referred in June 1974 to the Kagoshima University Hospital for investigation of muscular atrophy. He seemed to have been well until the age of 7 years, when he noticed progressive clumsiness in running. He first noticed difficulty in climbing stairs at the age of 17 years. One year before admission, he developed difficulty in getting up by himself. He had no symptoms of cardiac disorder. The family history and past history were not contributory. He did not drink alcohol. On admission, he was well developed. The pulse was 64/min and regular. The blood pressure was 102/42 mmHg. No murmur was audible. Neurological examination disclosed weakness and atrophy of the proximal muscles of the extremities. The gait was waddling. The ankle jerks were slightly accentuated bilaterally.

Other deep tendon reflexes were not elicited. The sensory examination was normal. The electromyogram showed a neurogenic pattern. Muscle biopsy revealed mixed neurogenic and myogenic muscular atrophy. The nerve conduction velocity was normal. Blood picture, urinalysis, and blood chemistry were all within normal range. The chest *x*-ray film showed no cardiomegaly. The electrocardiogram was also normal. His bundle electrogram showed normal PA, AH, and HV intervals. Right cardiac catheterisation showed normal pressures. No shunt was seen.

METHODS

After informed consent was obtained, a Konno-Sakakibara catheter bioptome (Konno and Sakakibara, 1963) was inserted into the right ventricle through the right saphenous vein, and endomyocardial biopsy was performed.

Histological sections of the biopsy specimen were stained with haematoxylin and eosin. For electron microscopical observation, the tissue was fixed in 3 per cent glutaraldehyde buffered with 0·1 M phosphate (*p*H 7·4) for 2 hours and postfixed in 2 per cent osmium tetroxide for 2 hours. After rapid dehydration with ethanol and propylene oxide, the tissue was embedded in Epon 812. A Porter-Blum ultramicrotome (Ivan Sorvall, Inc.) was used for cutting the blocks and the sections were stained on the grids with uranyl acetate and lead citrate. Electron micrographs were taken with a JEM 100B electron microscope.

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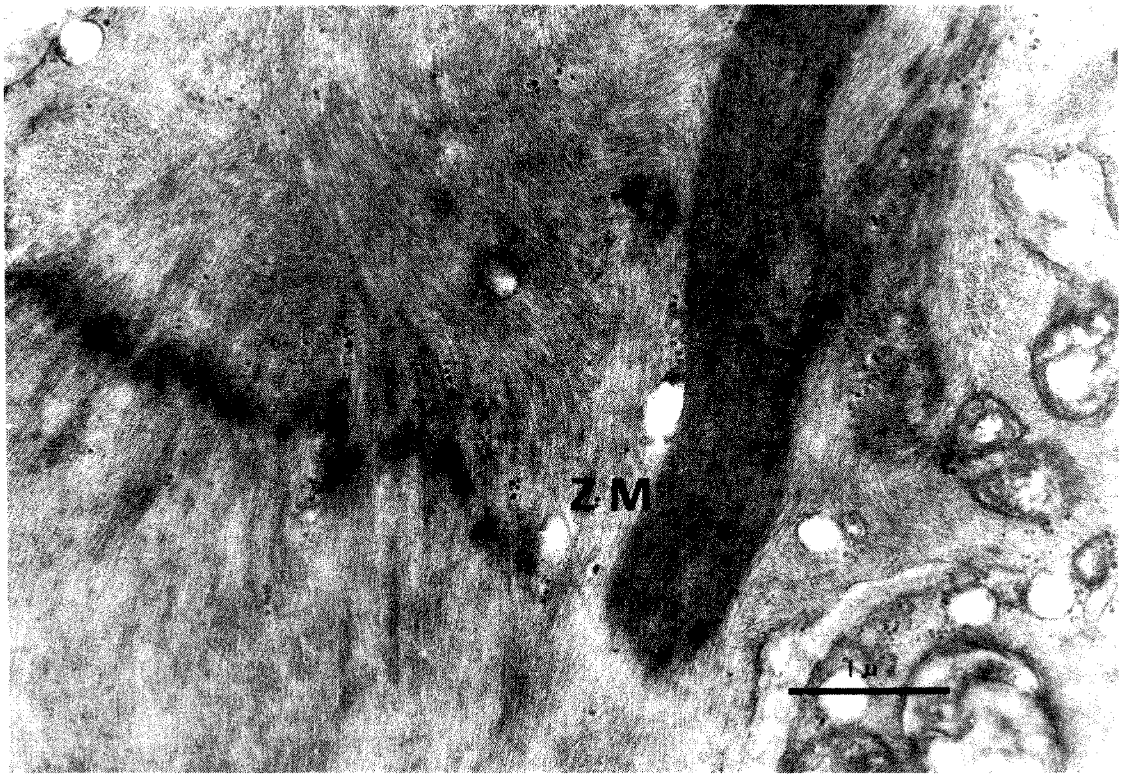

Fig. 1 *Electron micrograph showing fine filaments and abnormality in the Z band. Many fine filaments are packed within the cytoplasm. Some of them are attached almost perpendicularly to the irregular Z-band-like material. The fine filaments are 60 to 80 Å in diameter. The Z-band-like material (ZM) is present in an irregular band and in a cylindrical mass. A few degenerated mitochondria are also present.*

Results of morphological examinations

(A) LIGHT MICROSCOPICAL EXAMINATION

The specimen showed normal structure. No significant changes were observed in myocardial cells, the interstitial tissues, or in the endocardium.

(B) ELECTRON MICROSCOPICAL EXAMINATION

Degenerated myocytes were occasionally found among apparently normal myocytes. The degenerated myocytes contained many fine filaments, accumulations of Z-band-like material, a few abnormal mitochondria and some vesicles. The Z-band-like material was present in irregular bands or in cylindrical masses. A great many fine filaments were packed within the cytoplasm. Some of them were attached to the Z-band-like material almost perpendicularly. Thick filaments were very few or completely lost in these cells (Fig. 1). The fine filaments seemed to be actin filaments because of their perpendicular attachment to Z-band-like material and because of their diameter (60 to 80Å). A few mitochondria characterised by cristolysis or swelling were scattered within these myocytes. The incidence of these myocytes was about 1 or 2 out of 50 myocytes. An additional finding was the presence of leptomeric fibrils, which consisted of dense bands and fine filaments that were attached perpendicularly to each band and had a regular periodicity of about 220 mμ (Fig. 2). The leptomeric fibrils were seen in myocytes which showed degenerative changes, including degeneration of the mitochondria and irregularity of the Z bands.

Discussion

Seven cases of the K-W syndrome with cardiomyopathy have been reported. Histological studies of myocardium in this syndrome were reported in 2 patients. Sugimura *et al.* (1973) reported a 23-year-old woman who showed first degree atrioventricular block, atrial premature beats, and

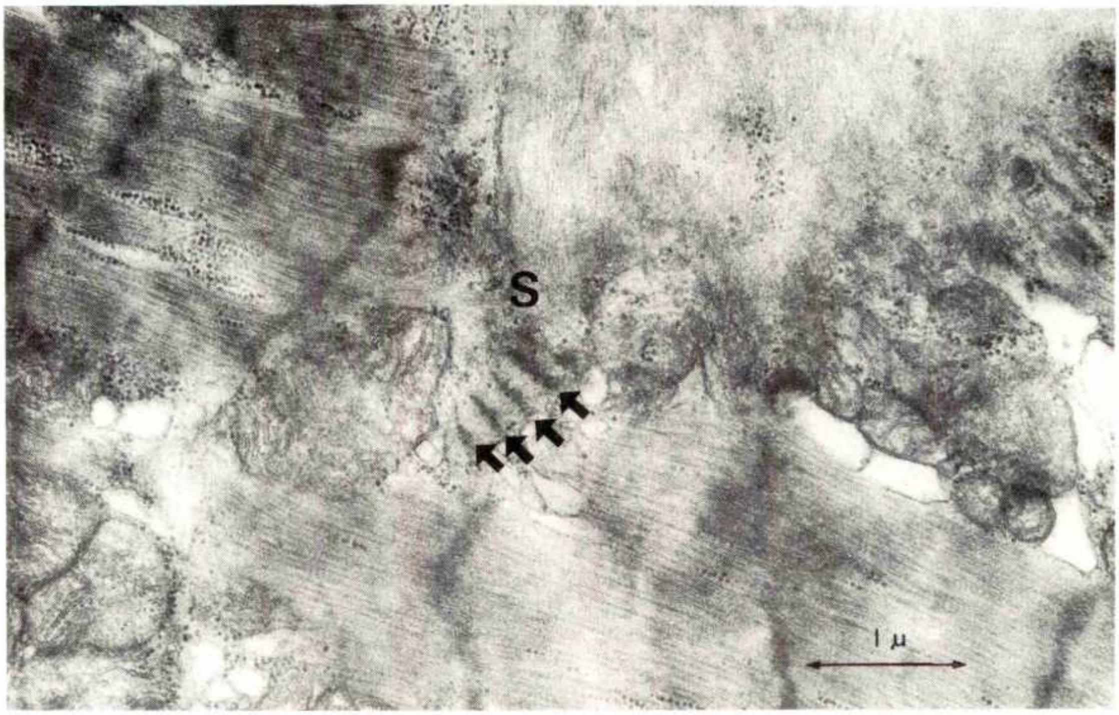

Fig. 2 *Electron micrograph showing leptomeric fibrils, which consist of dense bands (arrows) connected by fine filaments. They have a regular periodicity of about 220 mμ and seem to be connected to the sarcolemma (sectioned obliquely at S) on one side of the disorganised cell.*

paroxysmal atrial tachycardia. Fibrosis of the right atrium was shown by endomyocardial biopsy. Using light microscopy we noted slight interstitial fibrosis in the myocardium from another patient, a 26-year-old man with K-W syndrome and cardiac changes (Tanaka *et al.*, 1976). The present study, the first report on electron microscopical findings of the myocardium in K-W syndrome, has revealed preferential loss of myosin filaments in some degenerated myocytes. Recently, Maron *et al.* (1975) reported on ultrastructural changes of cardiac muscle cells in patients with cardiac hypertrophy. They reviewed the published reports on myofibrillar changes. Preferential loss of myosin filaments has been reported in various abnormal cardiac cells. It has been observed in cardiac muscle cells in hypoxic rats (Dusek *et al.*, 1971), in the crista supraventricularis in patients with congenital heart disease (Jones *et al.*, 1975), and in the left ventricle in patients who had received daunorubicin therapy (Buja *et al.*, 1973; Buja and Ferrans, 1975). However, this finding has not previously been reported in the myocardium of patients with heredofamilial-degenerative neuromyopathic diseases. We considered the preferential loss of myosin filaments found in this patient to be a degenerative change because other degenerative changes, including mitochondrial and Z band alterations, were also present in the myocytes.

Another finding seen in this patient was the presence of leptomeric fibrils. Leptomeric fibrils were discovered by Ruska and Edwards (1957) in the latissimus dorsi muscle of a young thrush in 1957. Since then, they have been found in myocardium as well as in the skeletal muscle of various mammals (Bogusch, 1975; Saetersdal and Myklebust, 1975). However, we have not found any previous report of leptomeric fibrils in human hearts. We also observed leptomeric fibrils in the myocardium of KK and yellow KK mice which were found to have myocardial degeneration (Nishi *et al.*). The function of the leptomeric fibrils is still controversial. The relation between the preferential loss of myosin filaments and the occurrence of leptomeric fibrils in our patient remains to be clarified.

References

Bogusch, G. (1975). Electron microscopic investigations on leptomeric fibrils and leptomeric complexes in the hen and pigeon heart. *Journal of Molecular and Cellular Cardiology*, **7**, 733–745.

Buja, L. M., and Ferrans, V. J. (1975). Myocardial injury produced by antineoplastic drugs. In *Recent Advances in Studies on Cardiac Structure and Metabolism*, Vol. 6, *Pathophysiology and Morphology of Myocardial Cell Alterations*, p. 487. Ed. by A. Fleckenstein and G. Rona. University Park Press, Baltimore.

Buja, L. M., Ferrans, V. J., Mayer, R. J., Roberts, W. C., and Henderson, E. S. (1973). Cardiac ultrastructural changes induced by daunorubicin therapy. *Cancer (Philadelphia)*, **32**, 771–788.

Dusek, J., Rona, G., and Kahn, D. S. (1971). Healing process in the marginal zone of an experimental myocardial infarct: findings in the surviving cardiac muscle cells. *American Journal of Pathology*, **62**, 321–338.

Jones, M., Ferrans, V. J., Morrow, A. G., and Roberts, W. C. (1975). Ultrastructure of crista supraventricularis muscle in patients with congenital heart diseases associated with right ventricular outflow tract obstruction. *Circulation*, **51**, 39–67.

Konno, S., and Sakakibara, S. (1963). Endomyocardial biopsy. *Diseases of the Chest*, **44**, 345–350.

Kugelberg, E., and Welander, L. (1956). Heredofamilial juvenile muscular atrophy simulating muscular dystrophy. *Archives of Neurology and Psychiatry*, **75**, 500–509.

Maron, B. J., Ferrans, V. J., and Roberts, W. C. (1975). Ultrastructural features of degenerated cardiac muscle cells in patients with cardiac hypertrophy. *American Journal of Pathology*, **79**, 387–434.

Matsumoto, K., Kakiuchi, F., Kakihana, M., Katayama, S., Sakamoto, T., and Murao, S. (1971). Kugelberg-Welander disease with cardiopathy of unknown etiology. Clinical report of a case. *Respiration and Circulation*, **19**, 863–870. (In Japanese with English abstract.)

Nishi, S., Tanaka, H., Shinyashiki, T., and Kanehisa, T. Histopathological studies of the myocardium in the spontaneously cardiopathic KK mice; a new disease model of idiopathic cardiomyopathy. (In preparation.)

Ruska, H., and Edwards, G. A. (1957). A new cytoplasmic pattern in striated muscle fibers and its possible relation to growth. *Growth*, **21**, 73–88.

Saetersdal, T. S., and Myklebust, R. (1975). Ulstrastructure of the pigeon papillary muscle with special reference to the sarcoplasmic reticulum. *Journal of Molecular and Cellular Cardiology*, **7**, 543–551.

Sterz, H., Harrer, G., Marchet, H., Kaserer, H. P., Schlamberger, H., Samec, Hj., and Stark, U. (1971). Primäre und neurogene Skelettmuskelerkrankungen bzw. -paralysen mit schweren Kardialen Rhythmusstörungen. *Zeitschrift für Kreislaufforschung*, **60**, 1–13.

Sugimura, F., Iijima, M., Ozawa, Y., Ooki, Y., and Watanabe, S. (1973). Two cases of Kugelberg-Welander's disease with cardiopathy. *Clinical Neurology*, **13**, 79–86. (In Japanese with English abstract.)

Tanaka, H., Uemura, N., Toyama, Y., Kudo, A., Ohkatsu, Y., and Kanehisa, T. (1976). Cardiac involvement in the Kugelberg-Welander syndrome. *American Journal of Cardiology*, **38**, 528–532.

Wohlfart, G., Fex, J., and Eliasson, S. (1955). Hereditary proximal spinal muscular atrophy. A clinical entity simulating progressive muscular dystrophy. *Acta Psychiatrica et Neurologica Scandinavica*, **30**, 395–406.

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Endocardial fibroelastosis and Niemann-Pick disease

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The concurrence of endocardial fibroelastosis and Niemann-Pick disease is described. This appears to be the first described case of endocardial fibroelastosis in association with a lipid storage disorder.

Endocardial fibroelastosis may be associated with many congenital heart malformations (Andersen and Kelly, 1956). Some cases occur in families in which the inheritance appears to be either multifactorial (Chen *et al.*, 1971) or of a more clearly defined pattern of inheritance, e.g. autosomal recessive (Rosahn, 1955), autosomal dominant (Hunter and Keary, 1973), and X-linked recessive (Westwood *et al.*, 1975). Endocardial fibroelastosis has also been described in association with some inborn errors of metabolism, notably the mucopolysacchari doses (Krovetz and Schiebler, 1972) and type II glycogen storage disease (Pompe's disease) (Stanbury *et al.*, 1972). It has not to my knowledge been described in association with a lipid storage disease. I wish to describe a case of endocardial fibroelastosis in Niemann-Pick disease.

Case report

This female infant was born to a 17-year-old single mother by breech delivery at 32 weeks' gestation and weighed 2295 g (5 lb 1 oz). The parents were gentile but unfortunately a detailed family history was not obtained. The child appeared to develop normally until the age of 2 months when it was noted that she was not acquiring normal head control. She lost interest in her surroundings, fed poorly, and failed to thrive over the next few months. At 6 months of age, while being treated for bronchopneumonia in hospital, gross hepatosplenomegaly was first noted. Before this there was no acute illness or overt evidence of myocarditis. She was referred for further investigation.

She was a small, thin, retarded 7-month-old infant. There was increased tone in the lower limbs, gross hepatosplenomegaly, and the heart was clinically enlarged. Blood pressure was 90 mmHg and the femoral pulses were palpable. There was an apical pansystolic murmur. Her fundi were normal.

INVESTIGATIONS

Haematology

Hb 10·5 g/dl; other haematological tests were normal.

Bone marrow

Bone marrow was cellular with storage cells with an amorphous cytoplasm suggestive of a lipid storage disease.

Liver function tests

Serum aspartate aminotransferase was 350 IU/litre; and serum alanine aminotransferase was 390 IU/litre. Other liver function tests gave normal results. Serum lipids were normal.

Chest x-ray

The radiograph showed cardiac enlargement with normal lung fields.

Electrocardiogram

There was pronounced left ventricular hypertrophy.

She developed pneumonia in hospital and died at 7½ months of age.

NECROPSY AND MORPHOLOGICAL FINDINGS

The liver and spleen were enlarged and contained foam cells which were also present in the bone marrow, adrenals, thymus, and alveoli. The lungs showed patchy collapse and consolidation. The heart was enlarged, weighing 75 g (normal 37 g). The left ventricular wall was thickened and showed endocardial fibroelastosis but there was no mononuclear infiltration of the myocardium. The aortic and mitral valve were not involved. There were no storage cells in the heart and the coronary arteries were normal. The brain was small, with atrophy of the white matter, and histology showed lipid in the nerve cells.

BIOCHEMICAL ANALYSES

Sphingomyelin was increased in both grey and white matter in the brain as well as in the visceral organs (see Table). Cholesterol and cerebrosides were decreased in white matter. These findings are typical of Niemann-Pick disease (Stanbury *et al.*, 1972). In addition, the thin layer chromatograms of gangliosides from cerebral cortex showed an increase in the G_{M_2} band and a faster-running NANA-containing glycolipid (probably G_{M_3}).

Discussion

This case includes all the typical features of type A Niemann-Pick disease (acute neuronopathic form) with early central nervous system involvement, gross hepatosplenomegaly, and death within the first four years of life (Stanbury *et al.*, 1972). The disease results from a defect in the activity of sphingomyelinase which results in the accumulation of sphingomyelin in brain and visceral organs. Though the enzyme assay is now widely used, unfortunately it was not available at the time these studies were conducted.

Our case is distinguished from others with type A Niemann-Pick disease by the concomitant occurrence of endocardial fibroelastosis. To our knowledge the association is unique. It has not been described in the excellent review by Fredrickson and Sloan (Stanbury *et al.*, 1972). Two further cases in Manchester, England, and 13 patients reviewed from the files of the Hospital for Sick Children, Toronto, Canada, had no cardiac involvement.

Theories on the aetiology of endocardial fibroelastosis include hereditary, viral, and mechanical. Other theories include myocardial hyperplasia, mitral regurgitation, anoxia, and a myocardial metabolic abnormality (Hutchins and Vie, 1972). Black-Schaffer (1957) originally proposed the mechanical hypothesis suggesting that endocardial fibroelastosis was a non-specific reaction of the endocardium to increased mural tension of whatever cause. Hutchins and Vie (1972) combined the viral and mechanical tension theories in his study of a series of cases developing endocardial fibroelastosis after myocarditis (possibly caused by Coxsackie B but not proven). They proposed that these patients developed ventricular dilatation as a result of myocarditis. While the inflammatory condition subsided the ventricular dilatation and compensatory hypertrophy continued, with subsequent mitral regurgitation and endocardial fibroelastosis developing secondary to the ventricular dilatation and increased mural tension. Endocardial fibroelastosis in association with mucopolysaccharidoses or type II glycogen storage disease probably results from infiltration of the myocardium by the mucopolysaccharides and glycogen, respectively, resulting in impaired myocardial function and ventricular dilatation.

The cause of endocardial fibroelastosis in our case is puzzling. There was no infiltration of the subendocardium or myocardium by foam cells, which could result in impaired myocardial functions and ventricular dilatation. There were also no cardiovascular abnormalities to account for the endocardial fibroelastosis and no mononuclear infiltrate in the myocardium.

Hutchins and Vie (1972) found mononuclear infiltrates in 70 per cent of their cases of endocardial fibroelastosis. They thought that these cases had had a prolonged illness which had begun with an unrecognised myocarditis. The inflammatory lesion had resolved at the time of death. It is difficult to suggest that our case can be explained in this fashion, however, for the total duration of the illness was only a few months and there was no mononuclear infiltrate of the myocardium.

Endocardial fibroelastosis in this case of Niemann-Pick disease may be related to the underlying disease though there is no microscopical evidence of this. It may have followed myocarditis or it may represent the idiopathic type and be purely the coincidental occurrence of 2 rare diseases. A genetic aetiology for endocardial fibroelastosis can still not be excluded because a detailed family history was

Table *Lipid composition of organs from child with Niemann-Pick disease (mg lipid/100 mg dry wt)*

Tissue	*Total phospholipid*		*Sphingomyelin*		*Total cholesterol*		*Total cerebroside*	
	Patient	*Normal**	*Patient*	*Normal**	*Patient*	*Normal**	*Patient*	*Normal**
Cerebral white matter	23·9	32·6	13·22	7·5	6·88	10·53	5·11	—
Cerebral grey matter	27·8	33·0	15·52	4·5	6·52	5·14	4·23	—
Liver	29·0	12·0	21·96	1·6	7·10	—	1·41	—
Spleen	29·7	15·0	25·19	3·2	7·95	—	1·43	—
Kidney	19·6	—	12·90	—	3·01	—	2·24	—

*Normal values from Lowden *et al.* (1967).

not obtained. If the parents were consanguineous, the possibility of the simultaneous occurrence of 2 rare genetically determined diseases would be considered.

I thank Dr. G. M. Komrower for allowing me to study this patient who was under his care at the Royal Manchester Children's Hospital, Manchester, Dr. H. Marsden for necropsy information, and the late Professor J. N. Cumings for necropsy biochemical results. I also thank Professor R. E. B. Hudson, Dr. R. D. Rowe, and Dr. J. A. Lowden for their help in the preparation of this paper.

References

Andersen, D. H., and Kelly, J. (1956). Endocardial fibroelastosis: I. endocardial fibroelastosis associated with congenital malformations of the heart. *Pediatrics*, **18**, 513–538.

Black-Schaffer, B. (1957). Infantile endocardial fibroelastosis. *Archives of Pathology*, **63**, 281–306.

Chen, S., Thompson, M. W., and Rose, V. (1971). Endocardial fibroelastosis: family studies with special reference to counseling. *Journal of Pediatrics*, **79**, 385–392.

Hunter, A. S., and Keary, A. J. (1973). Primary endocardial fibroelastosis, an inherited condition. *Archives of Disease in Childhood*, **48**, 66–69.

Hutchins, G. M., and Vie, S. A. (1972). The progression of interstitial myocarditis to idiopathic endocardial fibroelastosis. *American Journal of Pathology*, **66**, 483–492.

Krovetz, L. J., and Schiebler, G. L. (1972). Cardiovascular manifestations of the genetic mucopolysaccharidoses. In *Birth Defects: Original Article Series*, Vol. VIII, No. 5, pp. 192.

Lowden, J. A., La Ramee, M. A., and Wentworth, P. (1967). The subacute form of Niemann-Pick disease. *Archives of Neurology*, **17**, 230–237.

Rosahn, P. D. (1955). Endocardial fibroelastosis: old and new concepts. *Bulletin of the New York Academy of Medicine*, **31**, 453–472.

Stanbury, J. B., Wyngaarden, J. B., and Fredrickson, D. S. (1972). *The Metabolic Basis of Inherited Disease*, 3rd ed. McGraw-Hill, New York.

Westwood, M., Harris, R., Burn, J. L., and Barson, A. J. (1975). Heredity in primary endocardial fibroelastosis. *British Heart Journal*, **37**, 1077–1084.

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IMPORTANT NOTICE

CARDIOVASCULAR RESEARCH

From January 1978 the number of issues published each year for CARDIOVASCULAR RESEARCH will be increased from 6 to 12. This change in frequency is prompted by the demand by authors and readers for more papers on the study of the heart circulation. The publication of 12 issues in 1978 incurs greater cost and the annual subscription rate is to be increased to:

Inland £30·00; Overseas US$60·00

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1. Postgrad. Med. J., 51, 10, (1975)
2. Danish Med. Bull., 21, 63, (1974)
3. Clin. Pharm. Ther., 15, 141, (1974)
4. J. Int. Med. Res., 2, 314, (1974)
5. Brit. J. Clin. Prac., 28, 311, (1974)
6. Brit. J. Clin. Prac., 29, 7, (1975)
7. Postgrad. Med. J., 51, (Suppl. 6), 54, (1975)
8. Brit. J. Clin. Prac. 30, 11-14 (1976)
9. Leading Article, Brit. Med. J., 2, 521, (1975)
10. J. Int. Med. Res., 3, 241, (1975)
11. Postgrad. Med. J., 51, (Suppl. 6), 71, (1975)
12. Acta. Med. Scand., 193, 119, (1973)
13. J. Int. Med. Res., 3, 104, (1975)
14. J. Int. Med. Res., 4, 37-41 (1976)

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